THE SYNTHESIS AND PROPERTIES OF CYCLOPROPYL-FUSED BICYCLO-[2.2.2]-OCTANE DERIVATIVES

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THE SYNTHESIS AND PROPERTIES OF CYCLOPROPYL-FUSED BICYCLO-(2.2.2)-OCTANE DERIVATIVES

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SUMMARY

For Intramolecular cyclopropane-electrophilic interactions, previous workers have attempted to investigate the electronic effects of cyclopropane ring in cyclopropyl carbinyl, 1-cyclopropylvinyl, homocyclopropylcarbinyl, cyclopropyl-fused norbornyl, spiro-cyclopropyladmantyl, and tricyclyl systems. Four different factors by which cyclopropyl ring may affect a reaction center have been recognized. These are: (1) conjugation effect; (2) homoconjugation and participation effects; (3) steric and strain effects; (4) inductive and field (nonconjugative) effects.

In order to investigate the various effects of cyclopropane ring, a rigid bicyclo-[2.2.2]-octane model system has been chosen. This research deals with the preparation of a series of isomeric 5,6-cyclopropyl-fused bicyclo-[2.2.2]-octane 2-carboxylic acids, 2-carboxylic esters, and 2-carbinyl tosylates, and the determination of their reactivities.

It is clear that steric effect in S_n1 reactions is not so important as in S_n2 reactions. The participation effect seems to be related to the solvolytic reactions in bicyclo-[2.2.2]-octane system

more significantly than do field effect. However an "edge" substituted cyclopropane ring operates the effects more likely as an electron-donating group in bicyclo-[2.2.2]-octane system.

CHAPTER I

INTRODUCTION

The chemistry of cyclopropane has received much attention. This is due to the fact that three carbon atoms of the cyclopropane ring lie in a plane and the angle strain is expected to be considerable, since each carbon valence angle must be deformed 49.5° from it's "normal" value. [1] It is likely that some relief from the strain associated with the eclipsing of the hydrogens of cyclopropane is achieved by distortion of the H-C-H and H-C-C bond angle. The deviation of bond angles from the "normal" tetrahedral value causes the molecules to be strained, and hence to be unstable compared with molecules in which the bond angles are tetrahedral. The cyclopropane undergoes ring-opening reactions since these relieve the strain and yield the stable open chain compounds. The strain in cyclopropane can be evaluated quantitatively by comparison of the heats of combustion per CH_2 group. The heat of combustion for cyclopropane is 499.8 kcal/mole, [2] while the heat of combustion for open chain alkane is 157.4 kcal per CH_2. Hence the total strain for cyclopropane equals to $499.8 - 3 \times 157.4 = 27.6$ kcal. The Walsh model [3] (Figure 1) of cyclopropane has been used to recognize the atomic orbitals of the

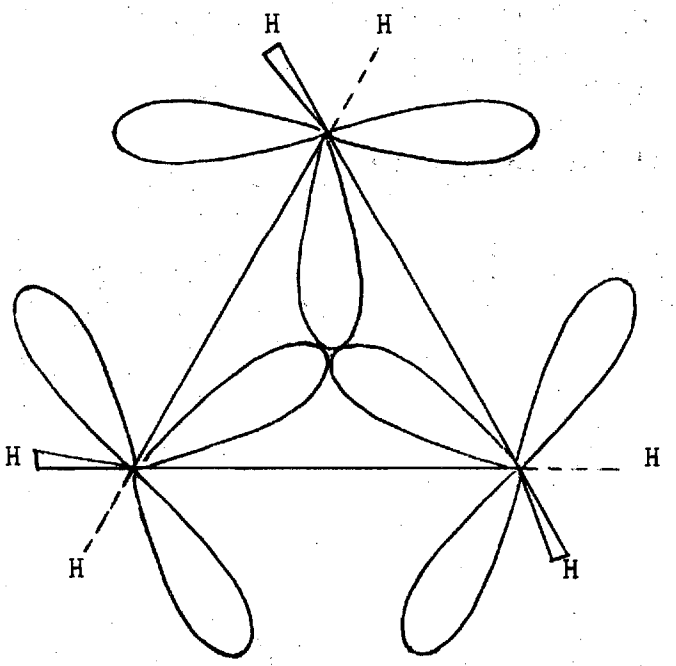


Figure 1. Walsh Model of Cyclopropane

deforming cyclopropane.

It is well known that the cyclopropane ring readily interacts with electrophiles. For intermolecular reactions, the cyclopropane ring opening has been achieved with halogens, [4] acylium ions, [5] and protons.[6] The extreme routes of electrophilic approach are toward the "face" of the ring and the "edge" of the ring. The Walsh model of cyclopropane predicts relatively high electron density of the "face" of the ring and the "edge" of the ring, the first associated with sp^2 orbitals directed toward the center of the ring, and the latter associated with p orbitals on the periphery of the ring. Although the "face" attack of the cyclopropane ring has been clearly predicted less favored than the "edge" attack, [7] the experimental results have not been in agreement with these predictions. In case of protonation of nortricyclene, recent results seem to favor "corner" protonated ion for the structurally stable intermediate. [8]

For intramolecular cyclopropane-electrophile interactions, the stabilities of a number of cyclopropyl derivatives have been well established. For different factors by which cyclopropyl ring may affect a reaction center have been recognized. These four factors are:

(1) Direct conjugation effects

(2) Homoconjugation effects

(3) Steric and strain effects

(4) Inductive and field effects

The above effects may be arbitrarily divided into two main catagories; steric and electronic effects. The following discussion will mainly focus on these effects and reveal their relative importance in the transmission of these effects from the cyclopropane ring to the reaction center.

The Conjugation Effect

Carbonium ions directly substituted with a cyclopropane ring are unusally stable and this is reflected in the fact that cyclopropylcarbinyl derivatives solvolyse with marked rate enhancement of when compared to the appropriate model systems. The nature and the extent of the extensive charge delocation from the carbinyl carbinyl carbon of cyclopropyl carbonium ion to the cyclopropane ring still remains unclear. The conjugation interaction of cyclopropane rings with adjacent carbonium ions was initiated by Schleyer [9] in his analysis of substituent effects on cyclopropyl carbinyl solvolysis rates. He reported the cyclopropyl carbinyl cations prefer the "bisected" conformation (Figure 2) which permit maximum overlap of p orbital of the carbon adjacent to the ring with cyclopropane "bend bonds". He used

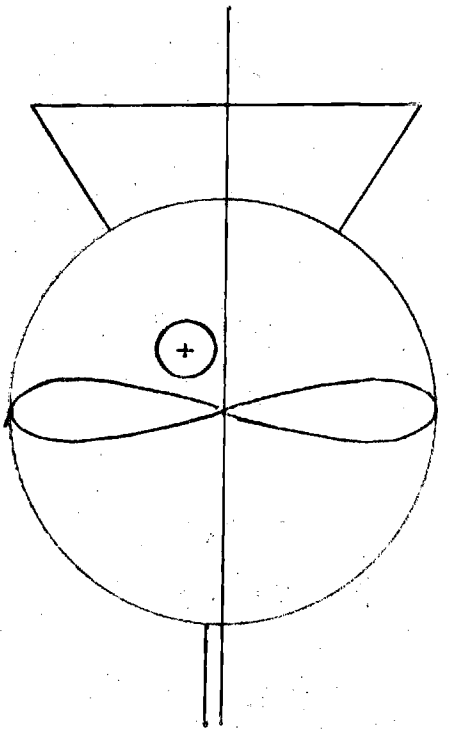
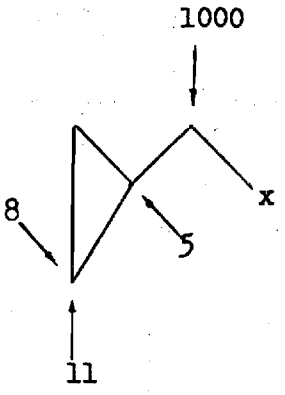


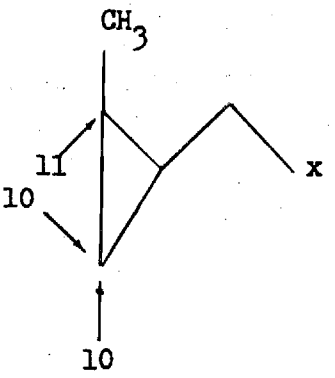
Figure 2. "Bisected" Conformation of Cyclopropane

methyl group as probes for charge delocalization in the transition states of cyclopropylcarbinyl solvolyses. The rate enhancements produced by substitution of a single methyl group in vaious positions is summarized in I. The effect of a second methyl group is shown in II and III. The methyl groups at C-2 and C-3 generated a markably constant multiplicative effect. The methyl results were clearly most consistant with symmetrical structure for cyclopropyl carbinyl cation transition state.

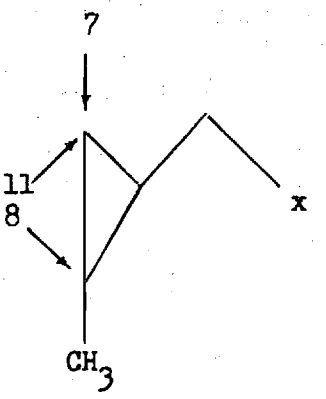
Bergman and Kelsey [10] have applied the extended Huckel molecular orbital method to examine the predicted properties of a number of 1-cyclopropylvinyl cations IV. The calculated energy difference between the extreme "bisected" and "perpendicular" conformations is 6.67 kcal/mole. The calculations suggested that the ions in all cases were most stable in the linear "bisected" conformation. Later, Bergman and Sherrod [11] reported that 1-cyclopropyl-1-iodoethylene underwent both siver-catalyzed and uncatalyzed solvolysis via the initial formation of the 1-cyclopropylvinyl cation IV. This ion appeared to be stabilized by delocalization of charge from the ionization center into the cyclopropane ring. On treatment with silver acetate in acetic acid, cis- and trans-1-cyclopropyl-1-iodopropene V and VI [12] give rise to product distributions which are identical with experimental error. The major



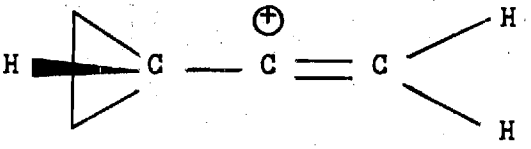
I



II

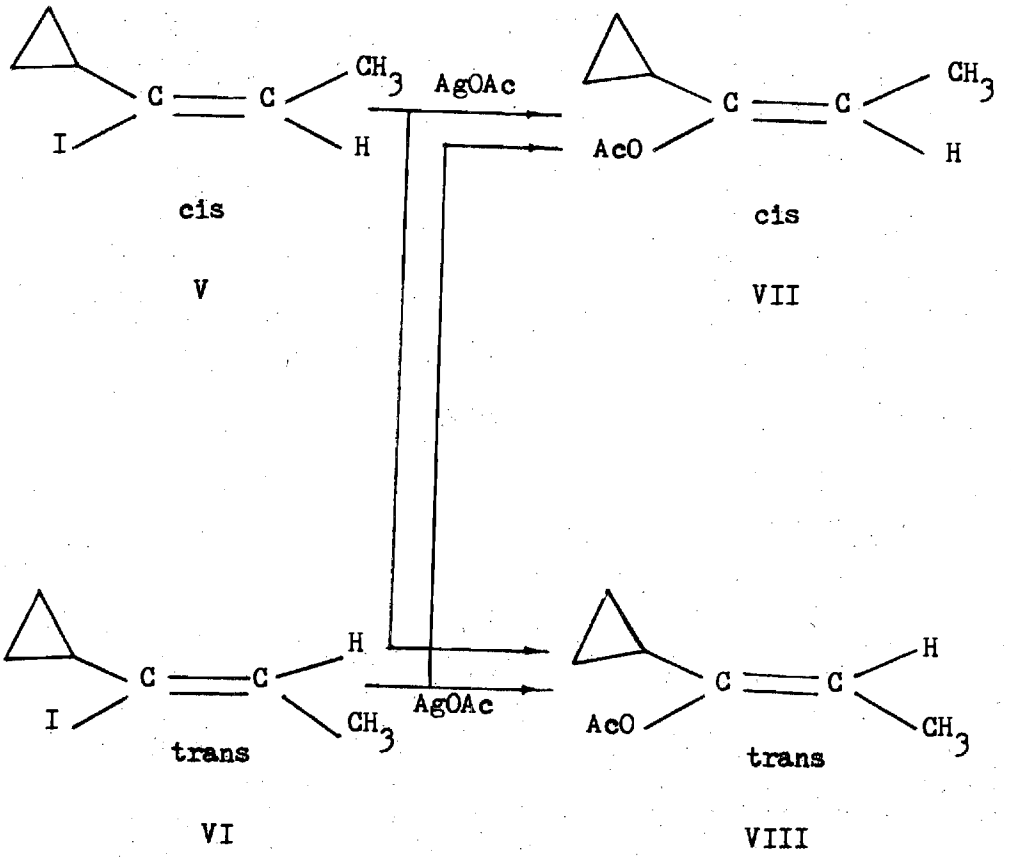


III



IV

SCHEME I



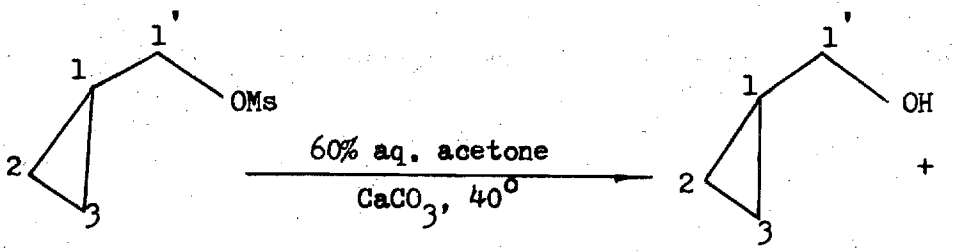
products in the mixture are the cis- and trans-1-cyclopropyl-1-acetoxypropenes VII and VIII. The linear cyclopropyl-2-methylvinyl cation was most likely the first formed intermediate in both ionizations.

Schleyer and Majerrski [13] investigated the stereochemistry of three different rearrangement processes involving the cyclopropylcarbinyl cation under solvolysis conditions. The substrate employed, cyclopropylcarbinyl-1,1',1'-trans-2,3,3-d_6-mesylate IX, contained only a single hydrogen atom as label, to facilitate nmr analysis of the solvolysis products (60% aqueous acetone, $CaCO_3$) cyclopropylcarbinyl-d_6 X, cyclobutanol-d_6 XI, and 1-buten-4-ol-d_6 XII. (Scheme II)

They found that the cis-2-hydrogens of IX was distributed in these products as follows. In X, 77% at the cis-2 (and cis-3) and 23% at the carbinyl (1') positions; in XI, 60% at the cis-2 (and cis-4) and 40% at the cis-3 positions; and in XII ca. 32% at the cis-1, ca. 30% at the 3, and ca. 38% at the 4- positions. Within experimental error all of these trans/cis ratios in X, XI, and XII were identical with that in the starting material, IX. This shows that the cyclopropylcarbinyl ⟶ cyclopropyl carbinyl, the cyclopropyl carbinyl ⟶ cyclobutyl, and cyclopropyl carbinyl ⟶ allylcarbinyl rearrangements all take place stereospecifically.

Quantitative nmr analysis of the proton signals from the sol-

SCHEME II

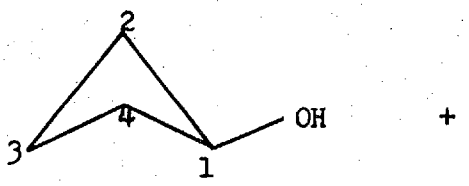


IX

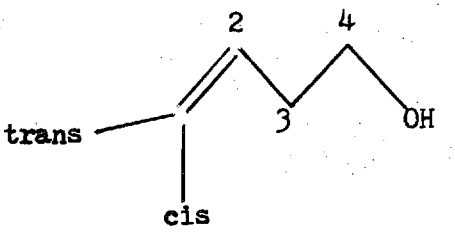
X (53%)

1, 10.0%
1', 1.9%
cis-2 or cis-3, 80.6% (91.5)
trans-2 or -3, 7.5% (8.5%)

1, 10.2%
1', 21.1%
cis-2 and -3, 62.2% (90.5%)
trans-2 and -3, 6.5% (9.5%)



+



XI (44%)

XII (3%)

cis-2 and -4, 48.8% (90.7%)
trans-2 and -4, 5.0% (9.3%)
cis-3, 32.8% (90%)
trans-3, 36% (10%)

cis-1, app. 26% (app. 90%)
trans-1, app. 3% (app. 10%)
2, app. 10%
3, app. 27%
4, app. 34%

volysis products from IX. The values given are the percentages of H at each position relative to the total carbon-bond H in each molecule. The value in parenthesis represent the cis-trans composition at key positions.

Schleyer and his coworkers [14] also reported this calculations of the rotational barrier in the n-propyl cation, both woth the extended and STO-3G basis sets, and in addition STO-3G calculations of the rotational barriers in the cyclopropyl carbinyl, and 1-methylcyclopropylcarbinyl cations.

Table 1 presents the results obtained with the extended basis set for the barrier to internal rotation about the C^+ - C bond in the n-propylcation. This rotational barrier is twofold and therefore on general grounds expected to be higher than the sixfold barrier in the ethyl cation (calculated to be close to zero). They found that the conformation in which the "empty" p lobe is coplanar with the C - C bond is favored by 2.3 kcal/mole. This indications is that C - C hyperconjugation which is most effective in this conformation is stronger than hyperconjugation involving the β-hydrogens.

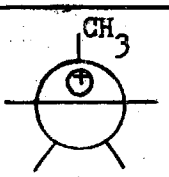
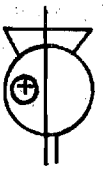
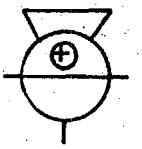
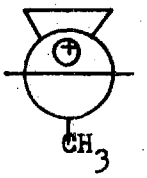
The STO-3G results for the same barrier but using a geometry derived from the optimized geometry of the ethyl cation are also shown

in Table 1. The barrier obtained with the two basis sets (2.52 and 2.26 kcal/mole) are in close agreement. The energy difference is 17.54 kcal/mole in the cyclopropyl-carbinyl XIV system. In going from the cyclopropylcarbinyl XIV to the 1-methylcyclopropylcarbinyl XV cation, this rotational barrier is reduced by 1.54 kcal/mole. The energy difference between the cyclopropylcarbinyl conformations XIVa and XIVb is revealed to be not a special case but only an extreme of a general phenomenon. When the C - C bonds are "bent", their p character and C - C hyperconjugative ability increase, but the enhancement in the rotational barrier only becomes really large when a three-membered ring is present.

The Homoconjugation Effects

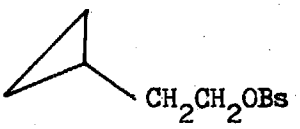
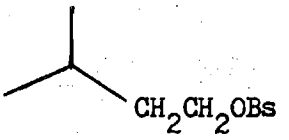
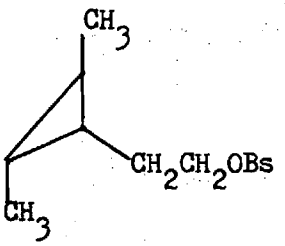
Sauers and Ubersax [15] have examined the formolysis of 2-cyclopropyl-1,1-d_2-ethyl brosylate and claim that the results can be explained "without recourse to intermediates with classical ones. If such intermediates are involved, they can not be the sole intermediates." It is apparent that their work could not be demontrated the presence or absence of participation. In view of their uncertainty, Rhodes and Takino [16] determined the rates of ethanolysis, acetolysis, and formolysis of 2-cyclopropylethyl brosylate XVI and isoamyl brosylate

Table 1. Extended ab initio and STO-3G Energies for Some Cations

Compound	Conformation	initio Extended ab Energy kcal/mole	STO-3G Energy kcal/mole	Relative Energy kcal/mole
XIIIa		-117.25566	-115.99294	(0.0) 0.0
XIIIb		-117.25206	-115.98893	(2.26) 2.52
XIVa			-153.37722	0.0
XIVb			-153.34926	17.54
XVa			-191.96189	0.0
XVb			-191.93640	16.00

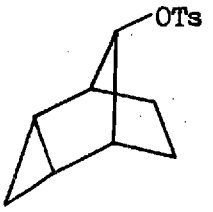
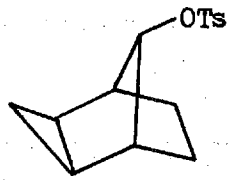
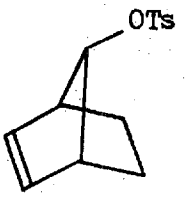
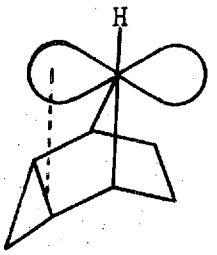
XVII, and found that they were virtually identical, indicating little or no rate enhancement by cyclopropane. Comparing the experimental results, they commented cyclopropane was a less effective neighboring group than an olefin, since allylcarbinyl brosylate is seven times more reactive than n-butyl brosylate.[17] Dewar and Harris[18] measured the rates of the formolysis of 2-cyclopropylethyl brosylate XVI and its dimethyl derivatives XVIII, and compared them with the corresponding rate for ethyl brosylate XIX (Table 2). They found that dimethyl substituted 2-cyclopropylethyl brosylate solvolysis about three times faster than 2-cyclopropylethyl brosylate must be attributed to participation of the cyclopropyl group, for introduction of methyl substituents into the β-position of simple alkyl tosylate,[19] and the same would surely be true for the corresponding brosylates. They thought 2-cyclopropylethyl brosylate should solvolyze more slowly than ethyl brosylate XIX, however, the rates of the two brosylates were identical. A difference of the rates would be expected if the reaction involved no participation, since cyclopropyl should exert an inductive effect analogous to that of unsaturated groups. They finally concluded that participation was unimportant in the formolysis of 2-cyclopropylethyl brosylate, but the cyclopropane was a potentially effective

Table 2. The Relative Rates for Formolysis of Some Brosylates

Compound		Relative Rate
XVI		0.93
XVII		0.85
XVIII		3.12
XIX	CH_3CH_2OBs	1.0

neighboring group, being able to participate if aided by methyl substitution. As mentioned above, the cyclopropyl seems to be a less effective neighboring group than an olefin. However, in the norbornyl system, XX solvolyzes [18] 10^3 times faster than analogous norbornenyl derivative XXII (Table 3). The evidence can not be attributed to a greater innate ability to participate on the part of cyclopropyl than of vinyl; this is presumably due either to ring strain or to the fact that the geometrical requirements for effective cyclopropane orbital overlap with a carbonium center are more stringent than the requirement for double bond participation. [20] If the cyclopropane-ring bonds are considered to be bent orbitals with a high degree of p character, these orbitals are in effect turned in toward each other on the cyclopropane ring and are therefore less available for overlap with a nearly center than are the orbitals of a double bond. The rate enhancement of XX can be also attributed by the greatest stabilization of XXIII. This stabilization is achieved by orienting an empty carbon 2p orbital so that it has appropriate symmetry for interaction with the p orbital on an adjacent edge of the ring. It might be difficult to interpret why cyclopropylnorbornyl derivative XXI solvolyses 10^{14} times slower than isomeric XX. However, Sargent

Table 3. The Relative Rates for Solvolysis of Some Tosylates

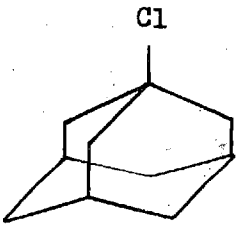
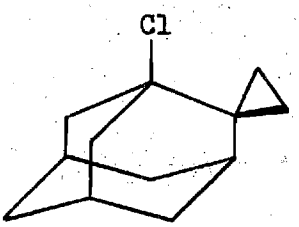
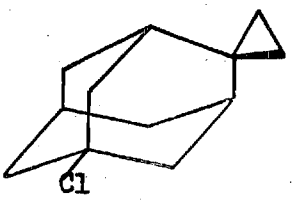
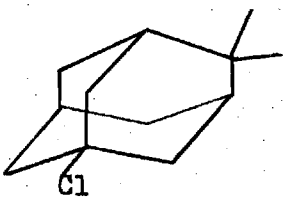
Compound		Relative Rate
XX		10^{3}
XXI		10^{-11}
XXII		1
XXIII		

and Taylor [20] suggested that nonbonded repulsive interaction of hydrogens on a cyclopropane ring with hydrogens attached to a carbonium ion center in the transition state for participation might prevent cyclopropane assistance in transition state and cause the deceleration of XXI.

The Steric and Strain Effects

Schleyer and Martin [21,22] determined the solvolysis rates of XXIV, XXV, XXVI and XXVII in 50 percent aqueous ethanol and found the results with XXV were very surprising (Table 4). Instead of rate enhancement usually associated with cyclopropylcarbinyl systems XXV reacted almost 10^3 more slowly than the model compound XXVI. This is due to the fact that XXV is held rigidly in a "perpendicular" conformation which is less stable than a "bisected" conformation by a considerable magnitude, variously estimated to be 9 to 22 kcal/mole.[23] During solvolysis, the developing orbital is constrained to be perpendicular to the cyclopropane ring. The stereochemistry in XXV is favorable for cyclopropylcarbinyl-cyclobutyl ring-ring expansion. Thus, there should be no assistance to ionization in XXV atall. The observed destabilization and rate depression can be presumably attributed to the orientation of the cyclopropane ring. The remotely

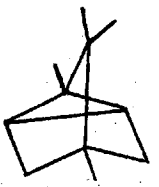
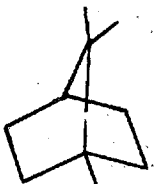
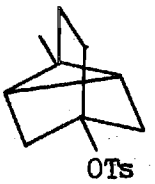
Table 4. The Relative Rates for Solvolysis of Some Chlorides

Compound		Relative Rate, 25°
XXIV		1.0
XXV		1.6×10^{-3}
XXVI		0.4
XXVII		0.6

substituted model compounds XXVI and XXVII solvolyze only slightly more slowly than 1-admantyl chloride XXIV, indicating no significant substituent effect to be present.

Bergman and Gleicher [24] observed that 4-tricyclyl trifluoromethanesulfonate XXVIII was approximately 10^{-4} times as reactive as its bicyclic analog apocamphy triflate XXIX (Table 5). The cyclopropane ring in this molecule afforded no stabilization to the interacting p orbital, and its presence appears to be responsible for the rate deceleration relative to its bicyclic analog XXIX and the tricyclic triflate XXX. In order to investigate the cause of this deceleration, they decided to use the method of Gleicher and Schleyer [25] to calculate the strain energies of XXVIII, XXIX and XXX. The calculated H_{strain} values for the nortricyclyl and tricyclyl systems were very large, and indicated that this was almost completely due to the distortion of carbon-carbon bond angles at and adjacent to the carbonic center. A plot of the calculated change in strain energy vs. the negatives of the log of the relative rate constants is shown in Figure 3 and is reasonably linear. The existence of such a correlation can be taken as evidence that the strain and steric effects play the important roles in solvolysis.

Table 5. The Relative Rates and Strain Energies of Some Tricyclic Triflates

Compound		$k_{rel}^{25^\circ}$	H_{strain} kcal/mole
XXVIII		1.0	31.3
XXIX		2.8×10^4	25.4
XXX		5.5×10^7	19.1

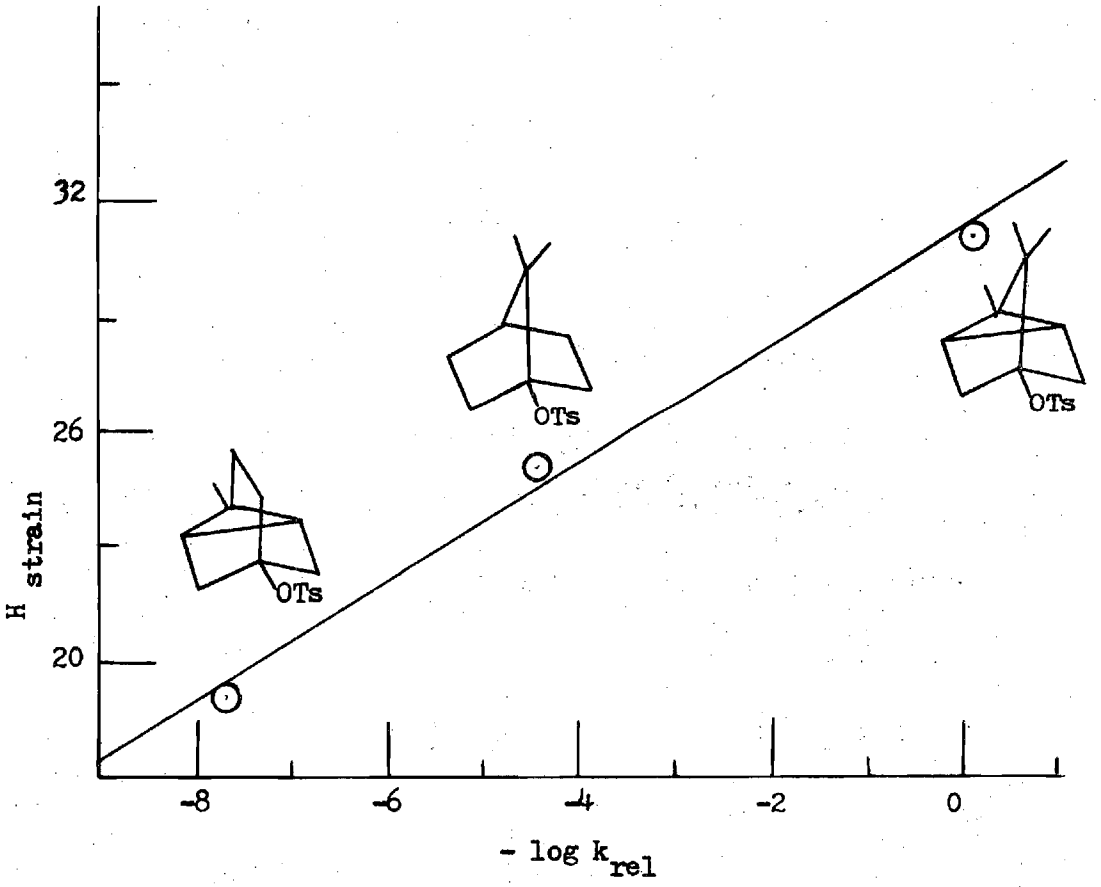


Figure 3. Plot of the Calculated Strain Energies of Ionization vs. Negative log of the Experimental Relative Rate Constants for Three Bridged Triflates

Sigma-Inductive and Field Effects

Sigma-inductive effect was originated by Derich [26] who defined the mechanism of transmission as the successive polarization of the sigma bonds. Consider a substituent at position s in a molecule. The polarization of the substituent-substrate bond may produce an effect at the carbon to which the substituent is attached. This effect may be transmitted to another position in the molecule $s^{+}- n$, n bonds removed from the point at which the initial effect was exerted, by the successive polarization of the intervening sigma bonds. The resulting effect at the reaction center will be quantitatively represented by the following equation (Equation 1)

$$\lambda_{s^{+}- n} = \lambda_{s\ p}(1/f)^{s^{+}- n} \qquad (1)$$

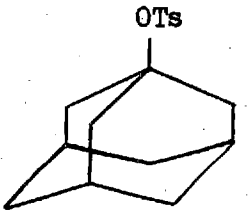
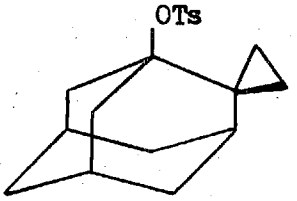
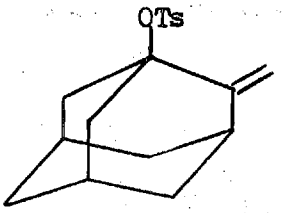
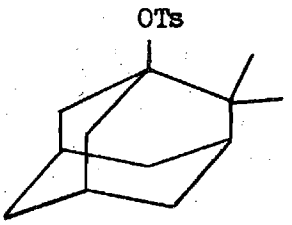
The resulting inductive effect at the reaction center, $\lambda_{s^{+}- n}$, will be equal to the initial inductive effect, λ_s, multiplied by a constant factor per bond, 1/f (1/f 1), and summed over all the pathways, p.

Martin and Ree [27] determined the acetolysis rates of a series of admantyl tosylate derivatives, XXXI, XXXII, XXXIII and XXXIV, and found the rates of cyclopropylcarbinyl and allyl tosylates, XXXII and

and XXXIII are slower than those of model compounds, XXXI or XXXIV by 10^2 and 10^4 respectively (Table 6). These results are in agreement with the previous conclusion that conjugative stabilization of a cation center by an adjacent "perpendicular" cyclopropyl ring or vinyl group is insignificantly small. They assume the deceleration could be attributed to (1) steric inhibition of solvent, (2) increased transition state angle strain for sp^2 hybridization at C-2 compared with sp^3 hybridization of XXXII, and XXXIII, (3) inductive transition state destabilization by the more electronegative cyclopropyl of vinyl group at C-2. They explained (1) is shown to be important by the fact acetolysis of XXXIV, which has the even bulkier gem-dimethyl at C-2. Explanation of (2) may contribute to the difference between XXI and XXII, but is insignificant in the comparison of XXXII and XXXI because of both have essentially sp^2 hybridization at C-2. They deemed inductive effect was the most reasonable explanation for the relative rates of admantyl tosylate derivatives.

Subsequently in a Hammet-Taft treatment, Martin and Ree[22] observed the linear correlation of the relative rates with the inductive substituent constants, σ_I, of XXXI, XXXII, XXXIII and XXXIV. A plot of log k_{rel} vs. σ_I is shown in Figure 4, and inductive sub-

Table 6. The Relative Rates for Acetolysis of Some Admantyl Tosylate Derivatives

Compound		Relative Rate, 45°
XXXI		1.0
XXXII		6.5×10^{-3}
XXXIII		8.8×10^{-5}
XXXIV		2.3

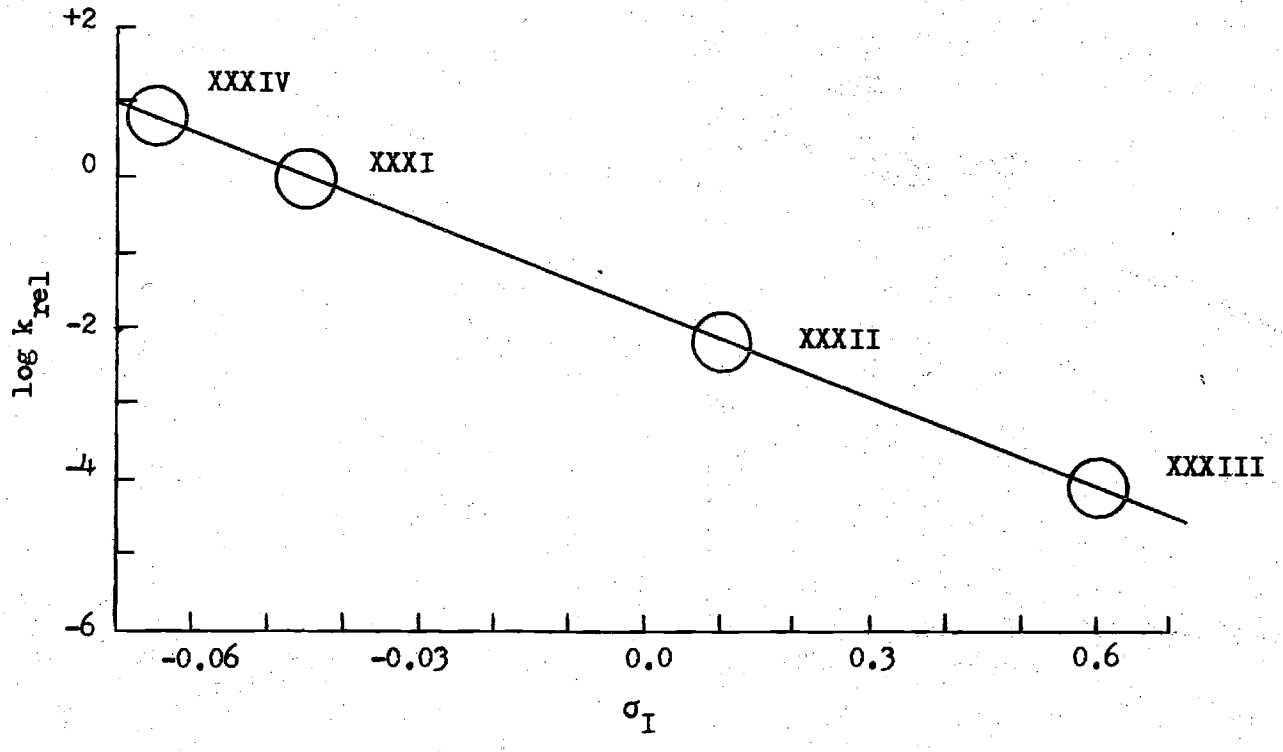


Figure 4. Hammet-Taft Plot for the Acetolysis of Admantyl Tosylate Derivatives

stituent constants [28] are listed in Table 7. This linear correlation observation convinced them the external cyclopropane bonds have the electro-withdrawing sp^2 character. However, this inductive effect should be very small by comparing the inductive substituent constant of cyclopropyl to hydrogen, + 0.01 to 0.0 (estimation of cyclopropyl Hammet-Taft $_I$ gives values ranging from +0.017 to 0.0, depending on the method of estimation used [29]). The facts that 2-cyclopropylethyl and isoamyl brosylates undergo ionization in a number of solvents at almost exactly the same rates, [16] and the pKa of m-cyclopropylbenzoic acid is about exactly the same as that of benzoic acid itself [29] support this inference. Moreover, if cyclopropyl is truly capable of exerting such a profound inductive effect, it is strange that this effect is not felt strongly in the 4-tricyclyl system, [24] where all three carbons of the cyclopropane ring are connected via methylene groups to the ionization center. Whether the cyclopropane ring exerts inductive effect to the reaction center in the above systems has generated significant controversy.

Besides the inductive effect, field effect is another factor to influence the trasmission of a polar of charged substituent to the reaction center through space. Eucken [30] reported the quantitative ex-

Table 7. Inductive Substituent Constants

Compound	Substituent	σ_I Aliphatic
XXXII	cyclopropyl	+ 0.01
XXXIII	vinyl	+ 0.06
XXXI	methyl	- 0.046
XXXVI	isopropyl	- 0.064

pression for the effect of dipolar substituent is as follows:

$$\log \frac{K_X}{K_H} = \frac{eu \cos \theta}{2.3\ kTR^2 D_e} \qquad (2)$$

Where e is the electronic charge, u is the difference in group or bond moment between the substituent and hydrogen, R is the distance from the center of the dipole to the ionizable proton, θ is the angle R makes with the direction of the bond moment, D_e is the effective dielectric constant, k is the Botzmann's constant, and T is the absolute temperature. At this juncture, noone has attempted to analyze the effects of a remote cyclopropyl on a reaction center in terms of electostatic (field) effects.

As mentioned above, the cyclopropane ring may exert various kinds of effect to the reaction center. However, the conjugation effect is only limited to the C2-substituted cyclopropane. Thus, the remaining effects can be considered are: (1) homoconjugative participation effect, (2) strain and steric effect, (3) δ-inductive effect. The inductive effect of the cyclopropane group is not easy to asses because of its strong tendency to interact conjugatively with reaction centers. The homoconjugative participation effect, contributed to the reaction center by an adjacent cyclopropane ring, of course, is

highly geometry dependent. Whether inductive effect of strain effect operates in admantyl systems has been argued for years. One therefore can not separate these effects from one another, the only thing one can recognize is which effect is the most powerful in a certsin system.

Accidentally, we found that the homocojugative participation effect seems to predominate over the others on a fused-cyclopropyl norbornyl system; inductive effect likely controls the reactivities in a corner-substituted admantyl derivatives; and the steric and strain effect rises high above the others in 4-tricyclyl systems, which has the cyclopropane ring facing to the reaction center.

In order to investigate the various effects of cyclopropane ring, we have chosen a rigid bicyclo-[2.2.2]-octane system. This thesis is dealing with the preparation of a series of isomeric 5,6-cyclopropyl-fused bicyclo-[2.2.2]-octane 2-carboxylic acids, 2-carboxylic esters, and 2-carbinyl tosylates, and the determination of their reactivities.

CHAPTER II

INSTRUMENTATION, EQUIPMENT, REACTANTS AND SOLVENTS

Instruments and Equipment

The spinning band column was a Nester/Faust Model 332 with a 1.5" by 28" column. Melting points were determined on a Mel-Temp apparatus and were uncorrected. Infrared spectra were recorded with Perkin-Elmer Infracord and Perkin-Elmer 457 grating spectrophotometers with solids on the form of potassium bromide pellets and liquids as thin films on sodium chloride plates. Nuclear Magnetic Resonance (nmr) spectra were recorded with a Varian A-60 and Varian A-100 spectrometers using the solvents specified. Chemical shifts reported in referenced to tetramethylsilane. The abbreviations s, d, t, q and m refer to singlet, doublet, triplet, quartet and multiplet, respectively, and are suffixed by the number of protons.

Gas-liquid chromatography (glc) was performed using an F and M Gas Chromatograph, Model 700, Model 750, with thermal conductivity detectors. Columns were six feet by one-eighth inch, six feet by three-quarters inch, stainless steel, and Pyrex glass with packings of 10%

SE-30, on firebrick, 3% Carbowax 20-M on Chromosorb W and 15% 1,2,3-tris-2-cyanoethoxypropane on 60/70 Gas Chromosorb P. Mass spectra were recorded using a Varian M-66 mass spectrometer. The evaporation was made on a Roto-Vac-Flash Evaporator from Buchler Instruments. Constant temperature baths were controlled by a Sargent Thermonitor. Column Chromatography was performed in a glass column using silica gel as absorbent.

Reagents and Solvents

Cyclohepta-1,3,5-triene was obtained from Aldrich Chemicals Incorporated and it was distilled before use. Ethyl acrylate was Eastman-Practical and it was not distilled before use. Ethyl acetate was Fisher Certified and it was used as obtained. Cyclohexene was Fisher (stabilized with sodium hydroxide) highest purity and it was not distilled before use. Bromine was obtained from Dow Chemical Company and it was use as obtained. Ethylene glycol was Fisher Certified and it was used as obtained. Sodium hydroxide was Baker analyzed reagent-pellets and it was used as obtained. Methylene iodide was obtained from Metal Hydrides, Incorporated and it was used as obtained. p-Toluenesulfonyl chloride was Fisher Certified and it was used as obtained. Silica gel was Fisher Certified (100-200 mesh) and it was used as obtained.

Benzene was Fisher Certified and it was distilled over calcium oxide before use. Chloroform was Fisher USP and Mallinkroft Technical and it was dried over calcium chloride before use. Ether was Fisher anhydrous and it was not distilled before use. Stocked 100 percent ethanol was refluxed with magnesium and it was distilled before use. Distilled water was redistilled from alkaline potassium permanganate with protection from carbon dioxide by an Ascarite tube.

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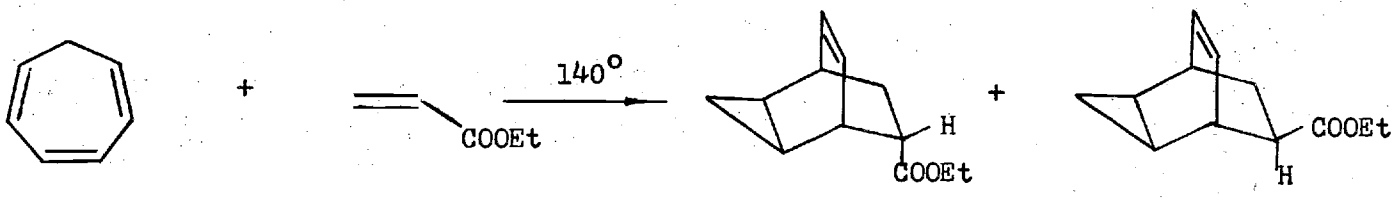
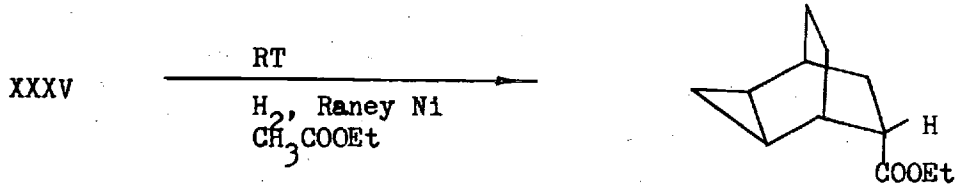


XXXV XXXVI



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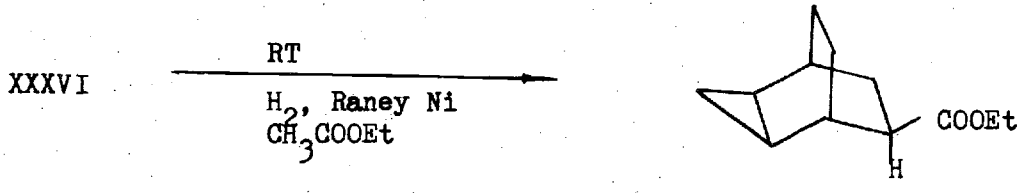

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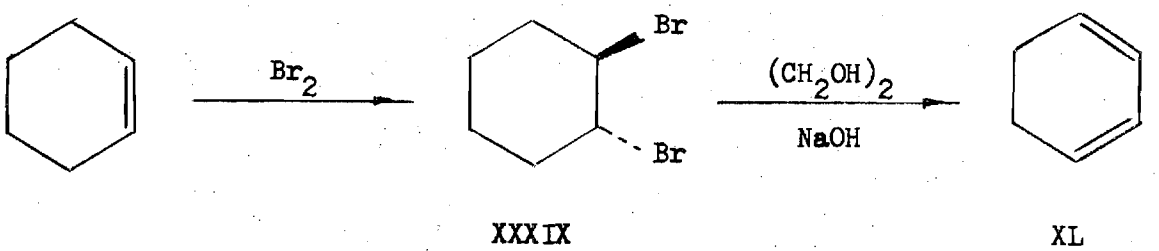

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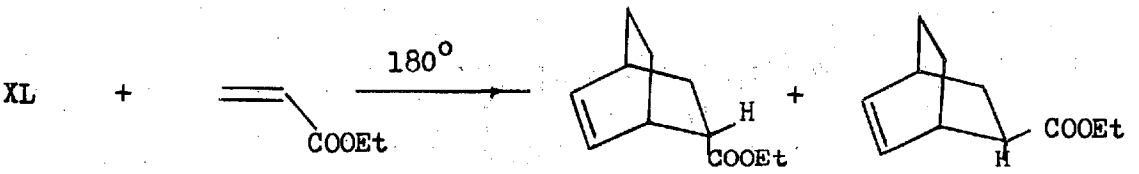

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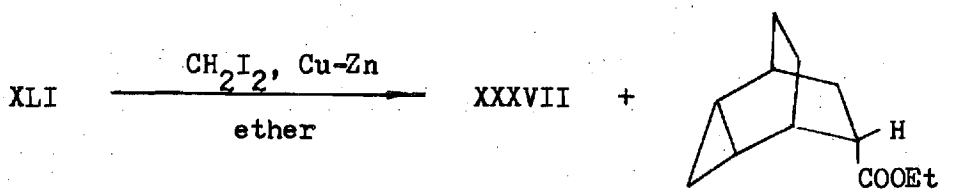

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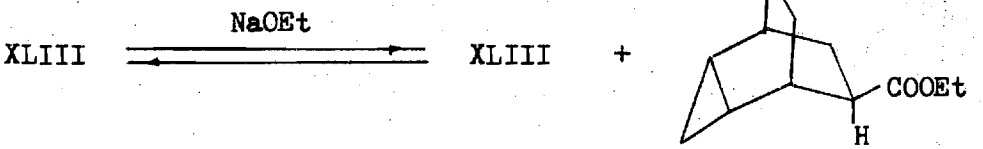

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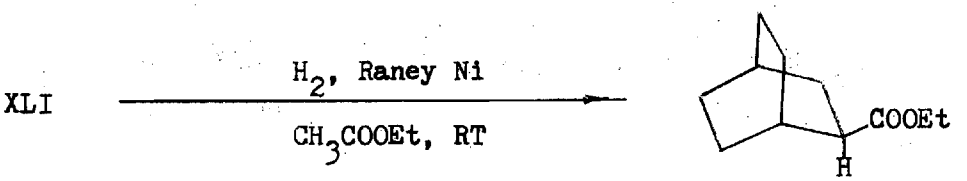

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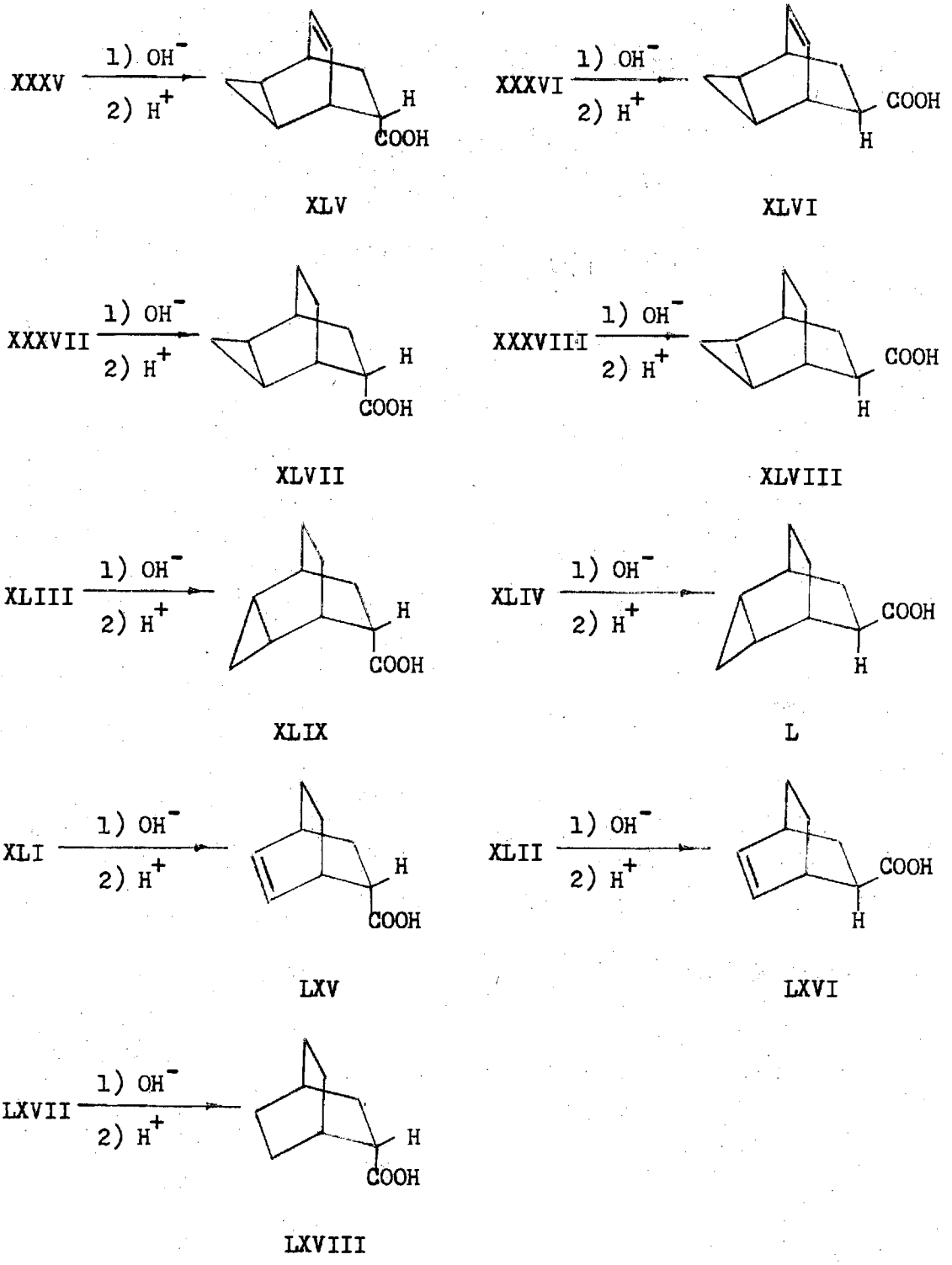
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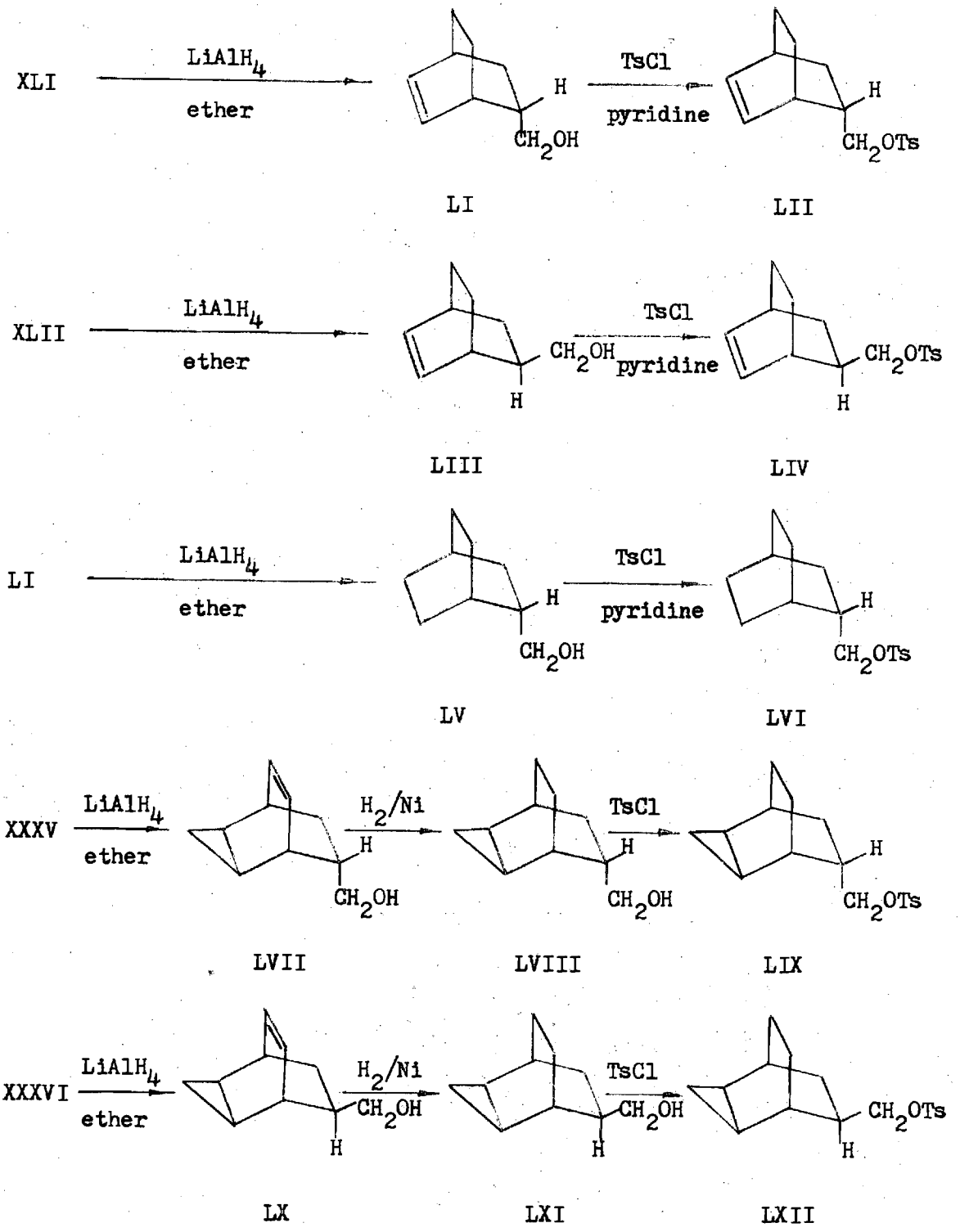
2) H⁺
H
COOH
XLV
XXXVI
1) OH⁻
2) H⁺
COOH
H
XLVI
XXXVII
1) OH⁻
2) H⁺
H
COOH
XLVII
XXXVIII
1) OH⁻
2) H⁺
COOH
H
XLVIII
XLIII
1) OH⁻
2) H⁺
H
COOH
XLIX
XLIV
1) OH⁻
2) H⁺
COOH
H
L
XLI
1) OH⁻
2) H⁺
H
COOH
LXV
XLII
1) OH⁻
2) H⁺
COOH
H
LXVI
LXVII
1) OH⁻
2) H⁺
H
COOH
LXVIII

SCHEME VI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LI
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pyridine
CH2OTs
H
LIII
LIV
LI
LiAlH4
ether
TsCl
pyridine
LV
LVI
XXXV
LiAlH4
ether
H2/Ni
TsCl
LVII
LVIII
LIX
XXXVI
LiAlH4
ether
H2/Ni
TsCl
LX
LXI
LXII

CHAPTER III

EXPERIMENTAL

Preparation of Cyclopropyl-fused Bicyclo-[2.2.2]-octane-2-carboxylic Esters, Acids, and 2-Carbinyl p-Tosylates

The preparation of cyclopropyl-fused bicyclo-[2.2.2]-octane-2-carboxylic esters, acids, 2-carbinyl p-tosylates is outlined in Schemes III, IV, V and VI.

Ethyl Tricyclo-[3.2.2.0 ^{2,4} endo]-non-8-ene-6-exo-carboxylate (XXXV) and Ethyl Tricyclo-[3.2.2.0 ^{2,4} endo]-non-8-ene-6-endo-carboxylate (XXXVI)

A solution of 46 g (0.50 mole) of cyclohepta-1,3,5-triene and 52 g (0.52 mole) of ethyl acrylate was placed into a thick-walled ampule, sealed, placed into a bomb [31] and heated for 140 hours at 140°C. The ampule was then allowed to cool to room temperature and broken open. The low boiling starting materials were removed under reduced pressure. Distilling of the remaining solution give 51 g (53.1 percent) of XXXV and XXXVI. The distillate contained 24 percent of XXXV and 76 percent of XXXVI as determined by glc (1,2,3-tris-2-

cyanoethoxy-propane, 108°C).

Distillation of 20.0 g of the isomeric mixture on a spinning band column gave partial separation of the isomers. The first fraction b.p. 74-76°C/0.03 mm had 3 g with approximately 70 percent endo-exo ester XXXV, 30 percent endo-endo ester XXXVI. The last fraction b.p. 80-82°C/0.03 mm had 2.5 g with approximately 5 percent endo-exo ester XXXV, 95 percent endo-endo ester XXXVI.

Complete separation of the isomers was carried out by preparative gas chromatography on a 72 x 3/4 inch column packed with 1,2,3-tris-2-cyanoethoxy-propane at 120°C using helium as a carrier.

In a typical separation, 3g of the mixture containing 70 percent ester XXXV, 30 percent ester XXXVI, was injected into the column about 15 times. The first peak was collected into the receiver to yield 1.3 g of pure endo-exo ester XXXV.

On the other hand, separation of 2.5 g of the isomeric mixture containing 5 percent ester XXXV, 95 percent ester XXXVI on preparative gas chromatography gave 0.9 g of pure endo-endo ester XXXVI.

Ethyl tricyclo-[3.2.2.0 $^{2.4}$ endo]-non-8-ene-6-exo-carboxylate XXXV was distilled, b.p. 64.5-64.8°C/0.03 mm; n_D^{20} 1.4914; retention time: 7.04 minutes (glc, 15 percent TCP, 108°C); ν_{max}^{neat} 3040, 2970, 2930, 2860, 1730, 1600, 1440, 1370 cm^{-1}; nmr (neat) τ: 4.10 (m,2),

5.76 (q,2), 6.83 (m,1), 7.17 (m,1), 7.60 (4d,1), 8.72 (t,3), 9.04 (m,2), 9.94 (2d,2); mass spectrum shows a parent ion peak at m/e 192 and a 100 percent peak at 92; exact mass: calcd. 192. 11494, found 192.12558; elemental analysis: calcd. C 74.97, H 8.39; found C 74.80, H 8.45.

Ethyl tricylo-[3.2.2.0 $^{2.4}$ endo]-non-8-ene-6-endo-carboxylate XXXVI was distilled, b.p. 65.6-65.8°C/0.03 mm; n_D^{20} 1.4934; retention time: 9.14 minutes (glc, 15 percent TCP, 108°C); ν_{max}^{neat} 3040, 2970, 2930, 2860, 1730, 1600, 1440, 1370 cm^{-1}; nmr (neat) τ: 4.22 (m,2), 5.94 (q,2), 6.81 (m,1), 7.22 (m,1), 7.35 (4d,1), 8.24 (m,2), 8.82 (t,3), 9.07 (m,2), 9.97 (2d,2); mass spectrum shows a parent ion peak at m/e 192 and a 100 percent peak at 92; exact mass: calcd. 192.11494, found 192.12686; elemental analysis: calcd. C 74.97, H 8.39; found C 74.79, H 8.51.

Ethyl Tricyclo-[3.2.2.0 $^{2.4}$ exo]-nonane-6-endo-carboxylate (XXXVII) and Ethyl Tricyclo-[3.2.2.0 $^{2.4}$ exo]-nonane-6-exo-carboxylate (XXXVIII)

Following a known procedure [32], a mixture of 12.4 g (0.0646 mole) of unsaturated endo-exo ester XXXV (24 percent) and endo-endo ester XXXVI (76 percent), 0.62 g of freshly prepared Raney Nickel W-2 [33], and 124 ml ethyl acetate, was hydrogenated at room temperature for 18 hours. The catalyst was filtered off and the solvent removed

in vacuo. Distillation yielded 11.6 g (93.5 percent) of the saturated exo-endo and exo-exo esters XXXVII and XXXVIII. Nmr spectrum gave no vinyl group absorption. Glc (1,2,3-tris-2-cyanoethoxy-propane column, 108°C) indicated the presence of 76 percent of exo-exo ester XXXVIII (retention time, 8.17 minutes) and 24 percent of exo-endo ester XXXVII (retention time, 9.32 minutes).

Ethyl Tricyclo-[3.2.2.0 ^{2,4} exo]-nonane-6-endo-carboxylate (XXXVII)

A mixture of 2.5 g (0.0130 mole) of tricyclic ester XXXV and 0.35 g of Raney Nickel W-2, which was previous made, and 50 ml of ethyl acrylate was placed in a pressure bottle. The bottle was then vibrated vigorously at room temperature for 18 hours, while the hydrogen was charged into the bottle continueously. The catalyst was filtered off and the solvent removed in vacuo. Distillation yielded 2.35 g (94 percent) saturated exo-endo ester XXXVII, b.p. 69.5-70.0°C/0.08 mm; n_D^{20} 1.4876; glc (1,2,3-tris-2-cyanoethoxy-propane column, 108°C) indicated the presenceof 99.4 percent XXXVII (retention time, 9.32 minutes); ν_{max}^{neat} 2995, 2935, 2865, 1730, 1445, 1385 cm^{-1}; nmr (neat) τ: 5.88 (q,2), 7.50 (4d,1), 7.71 (m,1), 7.95 (4d,1), 8.04 (m,1), 8.38 (4d,1), 8.70 (m,4), 8.77 (t,3), 9.15 (m,2), 9.54 (2t,1), 9.77 (2t,1); mass spectrum showed a parent ion peak at m/e 194 and a 100 percent peak at 94; elemental analysis: calcd. C 74.19, H 9.34; found C 74.25, H

9.38.

Ethyl Tricyclo-[3.2.2.0 ^{2,4} exo]-nonane-6-exo-carboxylate (XXXVIII)

Hydrogenation of 2.0 g (0.0104 mole) of tricyclic ester XXXVI was carried out in 20 ml of ethyl acetate using 0.20 g of Raney Nickel W-2 at room temperature for 18 hours. The catalyst was filtered off and the solvent removed in vacuo. Distillation yielded 1.88 g (94 percent) saturated exo-exo ester XXXVIII, b.p. 67.5-68.0°C/0.08 mm; n_D^{20} 1.4878; glc (1,2,3-tris-2-cyanoethoxy-propane column, 108°C) indicated 99.6 percent of XXXVIII (retention time, 8.17 minutes); nmr (neat) τ:5.91 (q,2), 7.36 (4d,1), 7.78 (m,1), 7.91 (4d,1), 8.10 (m,1), 8.33 (4d,1), 8.73 (m,4), 8.78 (t,3), 9.11 (m,2), 9.37 (2t,1), 9.67 (2t,1); mass spectrum showed a parent ion peak at m/e 194 and the 100 percent peak at 79; elemental analysis: calcd. C 74.19, H 9.34; found C 73.97, H 9.30.

1,2-Dibromocyclohexane (XXXIX)

A two liter, three-necked, round bottom flask, equipped with a magnetic stirrer, dropping funnel, and thermometer was charged with 500 g (6.10 moles) of cyclohexene and cooled in a dry ice-acetone bath.[34] Liquid bromine was added from the dropping funnel so that the temperature of the reaction remained below -10°C. Addition was stopped when a definite bromine color persisted. The product was dis-

tilled at reduced pressure to yield 688 g (2.840 moles) of XXXIX, b.p. 62°C/0.1 mm.

Cyclohexa-1,3-diene (XL) [34]

Five hundred millimeters of ethylene glycol was placed in a 3 liter, three-necked flask equipped with a stirrer, a thermometer whose bulb was in the liquid, a dropping funnel, a fractionating column, and a distilling head. Two hyndred and fifty grams (6.25 moles) of sodium hydroxide was added and the flask was heated and its contents stirred until they reached 230°C. At this point, 333 g (1.375 moles) of 1,2-dibromocyclohexane was added over a period of two hours, while a mixture of crude product and water distilled from the reaction mixture. The temperature in the reaction flask was kept between 220 and 230°C and that in the distilling head below 100°C. The 100 g of organic layer in the distillate was separated from water layer, dried over magnesium sulfate and fractionally distilled. Between 79 and 81°C, 110 g was collected.

Endo- and Exo-2-Carbethoxybicyclo-[2.2.2]-oct-5-ene (XLI) and (XLII)

A solution of 40 g (0.50 mole) of cyclo-1,3-diene, 52 g (0.52 mole) of ethyl acrylate was placed into a glass tube and cooled in dry ice-acetone and sealed. [35] The sealed tube was placed in a bomb and heated for 24 hours at 140°C. The tube was then cooled in dry ice/

acetone and broken open. The mixture was evacuated by water aspirator to remove low boiling starting materials. Distillation of the reaction product gave 56.5 g (62.8 percent) of XLI and XLII. The distillate contained 85 percent of endo and 15 percent of exo as determined by glc (1,2,3-tris-2-cyanoethoxy-propane, 101°C).

Distillation of 20 g exo-endo ester mixture with a 15-85 percent ratio on a spinning band column gave separation of endo ester XLI. The first fraction, b.p. 52-54°C/0.3 mm had 3 g with approximately 70-30 percent ratio exo-endo esters. The last fraction, b.p. 56-58°C /0.3 mm had 5 g of pure endo ester XLI. Separation of pure exo ester XLII was carried out on preparative gas chromatography by injecting 3 g of 70-30 percent ratio exo-endo esters into the column and the first peak was collected to yield 1.2 g of pure exo ester XLII.

Endo-2-carbethoxybicyclo-[2.2.2]-oct-5-ene XLI was distilled, b.p. 56.5-58.0°C/0.3 mm. Exo-2-carbethoxybicyclo-[2.2.2]-oct-5-ene XLII was distilled, b.p. 53.5-55.0°C/0.3 mm.

Ethyl Tricyclo-[3.2.2.0 $^{2.4}$ endo]-nonane-6-endo-carboxylate (XLIII) and Ethyl Tricyclo-[3.2.2.0 $^{2.4}$ exo]-nonane-6-endo-carboxylate (XXXVII)

Following a known procedure, [36] the reaction was carried out in a 500 ml three-necked round bottom flask equipped with a magnetic stirrer, reflux condenser and drying tube. A mixture of 15.6 g (0.213

mole) of zinc-copper couple,[37] 2.8 g (0.011 mole) of iodine, and 76 ml anhydrous ether was placed in the flask and stirred until the iodine color was faded. To this mixture, 44.2 g (0.165 mole) of methylene iodide and 19.8 g (0.110 mole) of unsaturated endo ester XLI were added. The stirred mixture was heated at gentle reflux for 68 hours. At the end of the reaction, most of the grey couple had been replaced by finely divided copper. The cooled mixture was filtered, and the filtrate was washed successively with cold 5 percent hydrochloric acid, 5 percent sodium bicarbonate solution and water. After the solution had been dried over anhydrous magnesium sulfate, ether and unreacted starting materials XLI were removed by distillation through a spinning band column. The residue was distilled to yield 9.85 g (50.8 percent) ofsaturated endo-endo ester XLIII and exo-endo ester XXXVII. Glc (1,2, 3-tris-2-cyanoethoxy-propane, 108°C) showed the presence of 71 percent of XLIII (retention time, 8.55 minutes) and 29 percent of XXXVII (retention time, 9.32 minutes).

Distillation a spinning band column gave partial separation of the isomers. The first fraction, b.p. 70-72°C/0.15 mm had 2.0 g with approximately 90 percent ester XLIII and 10 percent ester XXXVII. The last fraction, b.p. 73-75°C/0.15 mm, had 1.0 g with approximately 50 percent ester XLIII and 50 percent ester XXXVII. Separation of

pure ester XLIII was accomplished by injecting 2.0 g of the mixture containing 90 percent ester XLIII and 10 percent ester XXXVII into 1,2,3-tris-2-caynoethoxy-propane column at 115°C and the first peak was collected to yield 0.7 g of pure ester XLIII.

Ethyl tricyclo-[3.2.2.0 $^{2.4}$ endo]-nonane-6-endo-carboxylate XLIII was distilled, b.p. 68.5-69.5°C/0.08 mm; n_D^{20} 1.4874; retention time: 8.55 minutes (glc, 15 percent TCP, 108°C); ν_{max}^{neat} 3000, 2920, 2860, 1725, 1460, 1360 cm^{-1}; nmr (neat) τ: 5.87 (q,2), 7.52 (m,1), 7.73 (4d,1), 8.02 (m,1), 8.10 (m,1), 8.40 (m,4), 8.55 (m,1), 8.79 (t,3), 9.18 (m,2), 9.55 (2t,1), 9.84 (2t,1); mass spectrum showed a parent ion peak at m/e 194 and the 100 percent peak at 101; exact mass: calcd. 194.13058, found 194.13178; elemental analysis: calcd. C 74.19, H 9.34; found C 74.32, H 9.45.

Ethyl Tricyclo-[3.2.2.0 $^{2.4}$ endo]-nonane-2-exo-carboxylate (XLIV)

Epimerization [38] of ethyl tricyclo-[3.2.2.0 $^{2.4}$ endo]-nonane-2-endo-carboxylate XLIII was carried out by adding 20 ml of dry 0.5 N sodium ethoxide to 2.0 g of ester XLIII. This mixture was allowed to stir at room temperature for one week. One half of ethanol was removed in vacuo, the solution diluted with 40 ml of ice water and acidified with cold 0.5 N hydrochloric acid. The water layer was extracted with five 40 ml portions of ether, the ether extract dried over mag-

nesium sulfate and evaporated in vacuo. Glc (15 percent TCP, 108°C) indicated a composition of 26 percent ester XLIII and 74 percent ester XLIV. Separation of pure ester XLIV was achieved by injecting of 2.0 g of the mixture containing 26 percent ester XLIII and 74 percent ester XLIV into 15 percent TCP column on preparative gas chromatography at 115°C and the first half of the first peak was condensed to yield 0.7 g of pure ester XLIV.

Ethyl tricyclo-[3.2.2.0 ^{2,4} endo]-nonane-6-exo-carboxylate XLIV was distilled, b.p. 67.0-67.5°C/0.08 mm; n_D^{20} 1.4875; retention time: 8.02 minutes (glc, 15 percent TCP, 108°C); ν_{max}^{neat} 2995, 2930, 2860, 1730, 1460, 1370 cm^{-1}; nmr (neat) τ: 5.92 (q,2), 7.62 (m,1), 7.73 (m,1), 8.08 (m,1), 8.17-8.50 (m,2), 8.53 (m,4), 8.83 (t,3), 9.13 (m,2), 9.53 (2t,1), 9.74 (t,1); mass spectrum shows a parent ion peak at m/e 194 and the 100 percent peak at 79; exact mass: calcd. 194.13058, found 194.13368; elemental analysis: calcd. C 74.19, H 9.34; found C 74.26, H 9.41.

Tricyclo-[3.2.2.0 ^{2,4} endo]-non-8-ene-6-exo-carboxylic Acid (XLV)

Saponification of 0.9 g (0.004 mole) of endo-exo tricyclic ester XXXV was carried out by refluxing for 24 hours with 4 ml of a 50 percent aqueous ethanol solution of 2.0 N sodium hydroxide. Four ml of water were added and the solution extracted with three 15 ml portions

of ether to remove unreacted ester. The solution was acidified with four ml of 2.0 N hydrochloric acid at 0°C and then extracted with three 15 ml portions of ether. The ethereal extract was dried over magnesium sulfate and evaporated in vacuo. The residue was sublimed at 51°C, 0.4 mm, to yield 0.48 g (73 percent) of endo-exo acid XLV. m.p. 76.5-77.0°C; neutralization equivalent: calcd. 164.08; found 164.32; ν_{max}^{KBr} 3500-2500 (broad), 1700, 1460, 1370 cm^{-1}; mass spectrum showed a parent ion peak at m/e 164 and the 100 percent peak at 92; elemental analysis: calcd. C 73.14, H 7.37, found C 73.20, H 7.41.

Tricyclo-[3.2.2.0 ^{2,4} endo]-non-8-ene-6-endo-carboxylic Acid (XLVI)

Saponification of 1.2 g (0.006 mole) endo-endo tricyclic ester XXXVI was accomplished by refluxing 24 hours in 6 ml of 2.0 N sodium hydroxide in 50 percent aqueous ethanol. The mixture was diluted with 6 ml of water and extracted with three 20 ml portions of ether. The water layer was acidified with 2.0 N hydrochloric acid and extracted with three 20 ml of ether. The ether layer was dried over magnesium sulfate and evaporated in vacuo. The solid residue was sublimed at 36°C, 0.4 mm to yield 0.64 g (62 percent) white crystals, m.p. 60.5-61.0°C; neutralization equivalent: calcd. 164.08, found 164.36; ν_{max}^{KBr} 3500-2500, 1700, 1630, 1450, 1375 cm^{-1}; mass spectrum showed no peaks past

m/e 164 with a 100 percent peak at 92; elemental analysis: calcd. 73.14, H 7.37; found C 73.21, H 7.44.

Tricyclo-[3.2.2.0 $^{2.4}$ exo]-nonane-6-endo-carboxylic Acid (XLVII)

Saponification of 0.8 g (0.004 mole) exo-endo ester XXXVII was carried out by refluxing in 4 ml of 2.0 N sodium hydroxide in 50 percent aqueous ethanol for 24 hours. Then 4 ml of water were added to the reaction mixture and it was extracted with three 15 ml portions of ether to remove unreacted starting material. The mixture was cooled to 0°C and acidified with 4 ml of 2.0 N hydrochloric acid. The mixture was extracted with three 15 ml portions of ether. The exact was dried over magnesium sulfate and evaporated in vacuo. The solid was sublimed at 50°C, 0.3 mm, to yield 0.47 g (70 percent) of white crystalline exo-endo acid XLVII; m.p. 79.0-79.5°C; neutralization equivalent: calcd. 166.10, found 166.16; ν_{max}^{KBr} 3500-2500, 1700, 1470, 1340 cm^{-1}; mass spectrum showed a parent ion peak at m/e at 166 and a 100 percent peak at 94; elemental analysis: calcd. C 72.26, H 8.49; found C 72.00, H 8.53.

Tricyclo-[3.2.2.0 $^{2.4}$ exo]-nonane-6-exo-carboxylic Acid (XLVIII)

Saponification of 1.50 g (0.008 mole) ethyl tricyclo-[3.2.2.0 $^{2.4}$ exo]-nonane-6-exo-carboxylate XXXVIII was carried out by refluxing 24 hours in 8 ml of 2.0 N sodium hydroxide in 50 percent aqueous

ethanol. The mixture was diluted with 8 ml water and extracted with three 30 ml portions of ether. The water layer was cooled to 0°C and acidified with 8 ml of cold 2.0 N hydrochloric acid and extracted with three 30 ml portions of ether to remove dissolved acid. The ethereal extract was dried over magnesium sulfate and evaporated *in vacuo*. The residue was sublimed at 25°C, 0.5 mm, to yield 0.77 g (58 percent) of exo-exo acid XLVIII, m.p. 42.0-42.5°C; neutralization equivalent: calcd. 166.10, found 166.40; ν_{max}^{KBr} 3500-2500, 1695, 1470, 1340 cm^{-1}; mass spectrum showed a parent ion peak at m/e 166 and a 100 percent peak at 94; elemental analysis: calcd. C 72.26, H 8.49, found C 72.14, H 8.54.

Tricyclo-[3.2.2.0 $^{2.4}$ endo]-nonane-6-endo-carboxylic Acid (XLIX)

Saponification of 1.0 g (0.005 mole) ethyl tricyclo-[3.2.2.$0^{2.4}$ endo]-nonane-6-endo-carboxylate XLIII was accomplished by refluxing in 5 ml of 2.0 N sodium hydroxide in 50 percent aqueous ethanol for 48 hours. Five ml of water were added and the solution was extracted with three 20 ml portions of ether to remove unreacted ester. The water layer was acidified with 5 ml of hydrochloric acid and continueously extracted overnight with ether. The ethereal solution was dried over magnesium sulfate and evaporated *in vacuo*. The solid residue was sublimed at 42°C, 0.2 mm, to yield 0.56 g (65 percent) white

crystals, m.p. 63.5-64.0°C; neutralization equivalent: calcd. 166.10, found 166.38; ν_{max}^{KBr} 3500-2500, 1700, 1460, 1340 cm^{-1}; mass spectrum showed a parent ion peak at m/e 166 and a 100 percent peak at 94; elemental analysis: calcd. C 72.26, H 8.49, found C 72.32, H 8.50.

Tricyclo-[3.2.2.0 $^{2.4}$ endo]-nonane-6-exo-carboxylic Acid (L)

Saponification of 1.2 g (0.006 mole) ethyl tricyclo-[3.2.2.0 $^{2.4}$ endo]-nonane-6-exo-carboxylate XLIV was carried out by refluxing in 6 ml of 2.0 N sodium hydroxide in 50 percent aqueous ethanol for 48 hours. Then 6 ml of water were added to the reaction mixture and it was extracted with three 20 ml portions of ether to remove unreacted ester. The water layer was acidified with 6 ml of 2.0 N hydrochloric acid and extracted continuously with ether. The ether layer was dried over magnesium sulfate and evaporated in vacuo. The solid residue was sublimed at 80°C, 0.2 mm, to yield 0.52 g (51 percent) white crystals, m.p. 104.0-104.5°C; neutralization equivalent: calcd. 166.10, found 166.26; ν_{max}^{KBr} 3500-2500, 1700, 1460, 1340 cm^{-1}; mass spectrum showed a parent ion peak at m/e 166 and a 100 percent peak at 79; elemental analysis: calcd. C 72.26, H 8.49, found C 72.32, H 8.50.

Bicyclo-[2.2.2]-oct-5-ene-2-methyl Alcohol (LI)

Reduction of ethyl endo-bicyclo-[2.2.2]-oct-5-ene-2-carboxylate

XLI with lithium aluminum hydride gives bicyclo-[2.2.2]-oct-5-ene-2-endo-methyl alcohol LI. A certain amount of lithium aluminum hydride (2.84 g, 0.075 mole) was placed in a dry 50 ml, three-necked round bottom flask. It was fitted with a condenser, a magnetic stirrer, and a dropping funnel. All of this equipment was dried before being set up. A calcium chloride tube was connected in the end of the condenser to retard any passage of moisture from the air. The flask was immersed in an ice bath. Then 30 ml of absolute ether was added to the lithium aluminum hydride through the dropping funnel while stirring vigorously. Then the ice bath was removed and the lithium aluminum hydride slurry was allowed to reach room temperature. A solution of 4.50 g (0.025 mole) of ethyl bicyclo-[2.2.2]-oct-5-ene-2-endo-carboxylate XLI dissolved in 30 ml of absolute ether, was placed in the dropping funnel and added dropwise over a period of 10 minutes. During addtion, ice water was pumped through the condenser to condense the refluxing ether. The solution was refluxed for 48 hours and then cooled in an ice bath. Then 2.80 ml of cold water, 2.80 ml of 15 percent sodium hydroxide, and 8.5 ml of water were added to the solution in order and then the mixture was stirred at room temperature for one half hour. The solution was vacuum filtered through a sintered glass filter and the precipitate collected was washed five times with 10 ml portions of ether.

The ether solution was evaporated in vacuo. The residue solution was distilled to yield 2.73 g (79 percent) of alcohol LI, a viscous colorless liquid. b.p. 63.5-64.0°C/0.4 mm; n_D^{20} 1.5061; ν_{max}^{neat} 3600-3200, 3020, 2920, 2845, 1600, 1440, 1370, 1045, 710 cm^{-1}; mass spectrum showed a parent ion peak at m/e 138 and a 100 percent peak at 80.

Bicyclo-[2.2.2]-oct-5-ene-2-endo-carbinyl p-Toluenesulfonate (LII)

According to a known procedure, 1.0 g (0.007 mole) of bicyclo-[2.2.2]-oct-5-ene-6-endo-carbinol LI was dissolved in 10 ml pyridine in a 50 ml three-necked round bottom flask, which was fitted with a condenser, a low temperature thermometer, and a dropping funnel. The solution was cooled to -10°C in an ice-acetone bath. A solution of 1.38 g (0.007 mole) of p-toluenesulfonyl chloride, dissolved in 5 ml pyridine, was added dropwise to the alcohol solution. The temperature was kept at -4 to -10°C during the addtion. After completing the addtion, the solution was stirred for 30 minutes and was placed in the refrigerator for 24 hours. The pyrine was evaporated at room temperature using a water aspirator. The residue was added with vigorous stirring to a solution of 3 ml of concentrated hydrochloric acid and 10 g of ice. The tosylate LII precipitated and was filtered and dried. It was recrystallized from absolute methanol (10 ml per g) to yield 1.8 g (87 percent) of a white crystalline solid tosylate LII. m.p. 39.5-40.0°C;

ν_{max}^{KBr} 3020, 2920, 2860, 1600, 1440, 1370, 1340, 1175, 710 cm^{-1}; mass spectrum showed a parent ion peak at m/e 292 and a 100 percent paek at 80; elemental analysis: calcd. C 65.72, H 6.89, S 10.97, found C 65.48, H 6.92, S 10.83.

Bicyclo-[2.2.2]-oct-5-ene-2-exo-methyl Alcohol (LIII)

The ethyl bicyclo-[2.2.2]-oct-5-ene-2-exo-carboxylate XLII was reduced with lithium aluminum hydride to produce alcohol LIII. The procedure used was the same as the preparation of the alcohol LI. A solution of 1.25 g (0.033 mole) of lithium aluminum hydride in 15 ml of absolute ether was stirred vigorously at 0°C. A solution of 2.0 g (0.011 mole) of the ester XLII in 15 ml of absolute ether was added to the lithium aluminum hydride solution slowly and the mixture was refluxed for 70 hours. Then 1.25 ml of cold water, 1.25 ml of 15 percent sodium hydroxide, and 3.75 ml of water were added respectively to the mixture in a cold condition and the mixture was stirred for one half hour. Then the solution was filtered through a sintered glass filter by using water aspirator. The precipitate was washed five times with 10 ml portions of ether and the extract was evaporated in vacuo. The residue solution was distilled to yield 1.27 g (83 percent) of alcohol LIII. b.p. 60.0-60.5°C/0.4 mm; n_D^{20} 1.5093; ν_{max}^{neat} 3600-3200, 3020, 2930, 2840, 1600, 1440, 1370, 1050, 700 cm^{-1}; mass spec-

trum showed a parent ion peak at m/e 138 and a 100 percent peak at 80.

Bicyclo-[2.2.2]-oct-5-ene-2-exo-carbinyl p-Toluenesulfonate (LIV)

Bicyclo-[2.2.2)-oct-5-ene-2-exo-carbinol LIII was treated with p-toluenesulfonyl chloride to produce tosylate LIV. The procedure used was the same as the preparation of tosylate LII. A solution of 1.1 g (0.006 mole) p-toluenesulfonyl chloride in 4 ml pyridine was added slowly to a solution of 0.8 g alcohol LIII in 8 ml pyridine. The temperature was kept at -4 to -8°C during the addition. The solution was then stirred for 30 minutes and was placed in the refrigerator for 48 hours. The pyridine solution was added to a solution of 2.4 ml concentrated hydrochloric acid and 7.5 g ice. The tosylate LIV precipitated and was filtered and dried. It was recrystallized from absolute methanol (10 ml per g) to yield 1.17 g (69 percent) of a white crystalline tosylate LIV. m.p. 38.0-38.5°C; ν_{max}^{KBr} 3020, 2930, 2860, 1600, 1440, 1370, 1345, 1175, 700 cm^{-1}; mass spectrum showed a parent ion peak at m/e 292 and a 100 percent peak at 80; elemental analysis: calcd. C 65.72, H 6.89, S 10.97, found C 65.53, H 6.91, S 10.84.

Bicyclo-[2.2.2]-octane-2-methyl Alcohol (LV)

Hydrogenation of 1.1 g (0.008 mole) of the alcohol LI was carried out at 40 psi and at room temperature in 22 ml ethyl acetate with 0.055 g Raney Nickel W-2 as a catalyst. The mixture was shaked for

18 hours. The catalyst was filtered off, and the solvent was removed in vacuo. The residue solution was distilled under reduced pressure to yield 1.0 g (90 percent) of alcohol LV, a viscous colorless liquid. b.p. 64.5-66.0°C/0.05 mm; n_D^{20} 1.5010; ν_{max}^{neat} 3600-3200, 2930, 2850, 1440, 1365, 1065 cm^{-1}; mass spectrum showed a parent ion peak at m/e 140 and a 100 percent peak at 109; exact mass: calcd. 140.12003, found 140.12214.

Bicyclo-[2.2.2]-octane-2-carbinyl p-Toluenesulfonate (LVI)

Following a known procedure, a solution of 1.1 g (0.006 mole) p-toluenesulfonyl chloride in 4 ml pyridine was added slowly to a solution of 0.8 g alcohol LV in 8 ml pyridine. The temperature was kept at -2 to -7°C during the addtion. The solution was then stirred for 30 minutes and was placed in the refrigerator for 46 hours. The pyridine solution was added to a solution of 2.4 ml concentrated hydrochloric acid and 7.5 g ice. The tosylate LVI precipitated and was filtered and dried. It was recrystallized from absolute methanol (10 ml per g) to yield 1.42 g (85 percent) of a white xrystalline tosylate LVI. m.p. 50.0-50.5°C; ν_{max}^{KBr} 3020, 2935, 2860, 1600, 1450, 1360, 1340, 1180 cm^{-1}; mass spectrum showed a parent ion peak at m/e 294 and a 100 percent peak at 122; elemental analysis: calcd. C 65.27, H 7.53, S 10.89, found C 65.36, H 7.64, S 10.87.

Tricyclo-[3.2.2.0 $^{2.4}$ endo]-non-8-ene-6-exo-carbinyl Alcohol (LVII)

Following the procedure to produce alcohol LI, reduction of 2.8 g (0.015 mole of ethyl tricyclo-[3.2.2.0 $^{2.4}$ endo]non-8-ene-6-exo-carboxylate XXXV was accomplished in 20 ml ether by refluxing with 1.7 g (0.045 mole) of lithium aluminum hydride in 20 ml ether for 68 hrs. Then 1.7 ml of cold water, 1.7 ml of 15 percent sodium hydroxide, and 5.1 ml of water were added to the solution respectively and the mixture was stirred for 30 minutes. The precipitate was filtered off and washed with five 15 ml portions of ether. The ethereal solution was evaporated in vacuo. The residue solution was distilled under reduced pressured to yield 1.9 g (85 percent) of alcohol LVII. b.p. 74.5-76.5°C/ 0.08 mm; n_D^{20} 1.5258; retention time: 2.42 minutes (glc, 3 percent SE-30, 130°C); ν_{max}^{neat} 3600-3200, 3030, 2930, 2850, 1600, 1445, 1370, 1045, 700 cm^{-1}; mass spectrum showed no apparent parent ion peak at m/e 150, but a M - 18 ion peak at 132, and a 100 percent peak at 92; elemental analysis: calcd. C 79.95, H 9.39, found C 79.81, H 9.41.

Tricyclo-[3.2.2.0 $^{2.4}$ exo]-nonane-6-endo-carbinyl Alcohol (LVIII)

Hydrogenation of 1.6 g (0.011 mole) of tricyclo-[3.2.2.0 $^{2.4}$ endo]-non-8-ene-6-exo-carbinyl alcohol LVII was completed at 40 psi and room temperature in 32 ml ethyl acetate with 0.08 g Raney Nickel W-2 as a catalyst. The mixture was shaked vigorously for 18 hours.

The catalyst was filtered off and the solvent was removed in vacuo. The residue solution was distilled under reduced pressure to yield 1.5 g (93 percent) of alcohol LVIII. b.p. 77.0-78.0°C/0.05 mm; n_D^{20} 1.5175; retention time: 2.70 minutes (glc, 3 percent SE-30, 130°C); ν_{max}^{neat} 3600-3200, 2920, 2860, 1470, 1360, 1045 cm^{-1}; mass spectrum showed a parent ion peak at m/e 152 and a 100 percent peak at 94; exact mass: calcd. 152.12003, found 152.12089; elemental analysis: calcd. C 78.89, H 10.59, found C 78.66, H 10.65.

Tricyclo-[3.2.2.0 ^{2,4} exo]-nonane-6-endo-carbinyl p-Toluenesulfonate (LIX)

Following a known procedure, a solution of 1.5 g (0.008 mole) p-toluenesulfonyl chloride in 6 ml pyridine was added slowly to a solution of 1.2 g (0.008 mole) alcohol LVIII in 12 ml pyridine. The temperature was kept at -4 to -7°C during the addition. The solution was then stirred for 30 minutes and was placed in the refrigerator for 48 hours. The pyridine solution was added to a solution of 3.6 ml concentrated hydrochloric acid and 11 g ice. The tosylate LIX precipitated and was filtered and dried. It was crystallized from absolute methanol (10 ml per g) to yield 1.28 g (53 percent) of a white crystalline tosylate LIX. m.p. 30.0-30.5°C; ν_{max}^{KBr} 3000, 2925, 2860, 1590, 1440, 1360, 1340, 1175 cm^{-1}; mass spectrum showed a parent ion peak at m/e 306 and

a 100 percent peak at 134; elemental analysis: calcd. C 66.63, H 7.24, S 10.46, found C 66.51, H 7.29, S 10.37.

Tricyclo-[3.2.2.0 $^{2.4}$ endo]-non-8-ene-6-endo-carbinyl Alcohol (LX)

Following a known procedure, reduction of 3.5 g (0.018 mole) of ethyl tricyclo-[3.2.2.0 $^{2.4}$ endo]-non-8-ene-6-endo-carboxylate XXXVI was carried out in 30 ml ether by refluxing with 2.1 g (0.055 mole) of lithium aluminum hydride in 30 ml ether for 66 hours. Then 2.1 ml of cold water, 2.1 ml of 15 percent sodium hydroxide, and 6.3 ml of water were added respectively and the mixture was stirred for 30 minutes. The white precipitate was filtered off and washed with five 20 ml portions of ether. The ether extract was evaporated in vacuo. The residue solution was distilled under reduced pressure to yield 2.2 g (81 percent) of alcohol LX. b.p. 77.8-78.0°C/0.15 mm; n_D^{20} 1.5234; retention time: 2.18 minutes (glc, 3 percent SE-30, 130°C); ν_{max}^{neat} 3600-3200, 3030, 2920, 2850, 1600, 1430, 1375, 1040, 710 cm^{-1}; mass spectrum showed a parent ion peak at m/e 150 and a 100 percent peak at 92; exact mass: calcd. 150.10439, found 150.09453; elemental analysis: calcd. C 79.95, H 9.39, found C 79.94, H 9.45.

Tricyclo-[3.2.2.0 $^{2.4}$ exo]-nonane-6-exo-carbinyl Alcohol (LXI)

Hydrogenation of 1.9 g (0.013 mole) of tricyclo-[3.2.2.0 $^{2.4}$ endo]-non-8-ene-6-endo-carbinyl alcohol LXI was achieved at 40 psi and

room temperature in 38 ml ethyl acetate with 0.1 g Raney Nickel W-2 as a catalyst. The mixture was vibrated for 18 hours. The catalyst was then filtered off and the solvent was removed in vacuo. The residue solution was distilled under reduced pressure to yield 1.7 g (89 percent) of alcohol LXI. b.p. 80.0-81.0°C/0.18 mm; n_D^{20} 1.5183; retention time: 2.89 minutes (glc, 3 percent SE-30, 130°C); ν_{max}^{neat} 3600-3200, 2920, 2860, 1450, 1340, 1065 cm^{-1}; mass spectrum showed a parent ion peak at m/e 152 and a 100 percent peak at 79; exact mass: calcd. 152.12003, found 152.11196; elemental analysis: calcd. C 78.89, H 10.59, found C 78.72, H 10.61.

Tricyclo-[3.2.2.0 $^{2.4}$ exo]-nonane-6-exo-carbinyl p-Toluenesulfonate (LXII)

Following a known procedure, a solution of 1.5 g (0.008 mole) p-toluenesulfonyl chloride in 6 ml pyridine was added slowly to a solution of 1.2 g (0.008 mole) alcohol LXI in 12 ml pyridine. The temperature was kept at -4 to -8°C during the addition. The solution was then stirred for 30 minutes and was placed in the refrigerator for 44 hours. The pyridine solution was added to a solution of 3.6 ml concentrated hydrochloric acid and 11 g ice. The tosylate LXII precipitated and was filtered and dried. It was recrystallized from absolute methanol (10 ml per g) to yield 1.57 g (65 percent) of a white crystalline

tosylate LXII. m.p. 65.0-65.5°C; ν_{max}^{KBr} 3000, 2925, 2860, 1590, 1450, 1370, 1345, 1175 cm^{-1}; mass spectrum showed a parent ion peak at m/e 306 and a 100 percent peak at 91; elemental analysis: calcd. C 66.63, H 7.24, S 10.46, found C 66.40, H 7.23, S 10.43.

5-Iodo-6-Hydroxybicyclo-[2.2.2]-octane-2-endo-carboxylic Acid Lactone (LXIII)

Following a knowing procedure, [39] 0.5 g (0.003 mole) of bicyclo-[2.2.2]-oct-2-ene-5-endo-carboxylic acid XLI was dissolved in 18 ml of 0.5 M sodium bicarbonate to which 1.6 g of iodine and 2.9 g of potassium iodide dissolved in 9 ml water were added. The reaction mixture was kept in the dark and stirred overnight at room temperature. The stirring was then stopped and the mixture was allowed to settle. The supernatant solution was poured off and the black oil in the bottom of the flask dissolved in chloroform. The chloroform solution was decolorized by shaking with aqueous sodium thiosulfate solution, washed with 5 percent sodium bicarbonate solution and then washed with water. The oil layer was dried over magnesium sulfate and the chloroform removed in vacuo. The yellow residue was recrystallized from n-hexane to yield 0.53 g (58 percent) of white crystalline LXIII. m.p. 79.0-79.5°C. ν_{max}^{KBr} 3020, 2950, 2920, 2870, 1790, 1450, 1340 cm^{-1}; mass spectrum showed a parent ion peak at m/e 278 and a 100 percent peak at 79.

8-Iodo-9-endo-hydroxy-tricyclo-[3.2.2.0 $^{2.4}$ endo]-nonane-6-endo-carboxylic Acid Lactone (LXIV)

Iodolactonization of tricyclo-[3.2.2.0 $^{2.4}$ endo]-non-6-ene-8-endo-carboxylic acid XLVI carried out by dissolving 0.4 g (0.0024 mole) acid XLVI in 15 ml of 0.5 M sodium bicarbonate to which 1.3 g of iodine and 2.5 g of potassium iodide dissolved in 7 ml water were added. The reaction mixture was stirring continueously overnight at room temperature. The mixture was then allowed to settle. The oil layer was dissolved in chloroform. The chloroform solution was decolorized by adding aqueous sodium thiosulfate solution and shaking vigorously. The solution was then washed with sodium bicarbonate solution, water, and dried, and the chloroform was removed in vacuo. The residue was recrystallized from n-hexane to yield 0.35 g (49 percent) of white crystalline LXIV. m.p. 69.0-69.5°C; ν_{max}^{KBr} 3020, 2940, 2870, 1790, 1470, 1340 cm^{-1}; mass spectrum showed a parent ion peak at m/e 290 and a 100 percent peak at 127.

Zinc-Copper Couple [37]

An intimate mixture of 24 g of technical zinc dust and 3 g of cupric oxide was introduced into a 48- by 3/8- inches Pyrex tube placed horizontally and plugged with asbestos 5 inches from one end, and was spead evenly in the bottom half of the tube. A loose plug of asbestos

was inserted into the tube, and a steam of hydrogen was introduced. After the tube was thoroughly swept with hydrogen, it was placed in a 15 inches tube furnace. Heating was started first at the hydrogen entrance end of the tube, where, after 5 to 10 minutes, reduction became apparent. The furnace temperature at this time was maintain at 500 to 550°C. The tube was left in its original position until minute shining pellets were imbeded in the metal. Then the tube was moved so that the next section of zinc-copper oxide mixture was heated. At this time a faint red glow was observed, while the upper part of the tube became clouded with a film of condensed zinc. When all the material was reduced and the water driven from the tube, the latter was allowed to cool. The product was a gray color powder.

Measurement of the Rates of Alkaline Hydrolysis of the Isomeric Unsaturated Cyclopropyl-fused Esters, XXXV and XXXVI, and Saturated Cyclopropyl-fused Esters XXXVII, XXXVIII, XLIII and XLIV, and Saturated and Unsaturated Esters XLI, XLII and LXVII

The general procedure used to measure the rates of alkaline hydrolysis of the esters was described by Siegel and Karmarmy.[40] Two solutions of sodium hydroxide, 0.0395 N and 0.0187 N, were made up in 50 percent (by weight) aqueous ethanol and standarized to a phenol-

phthalein end point against potassium acid phthalate. A 0.0388 N hydrochloric acid in water solution was prepared and titrated against standarized sodium hydroxide solution. The ester solution was prepared by weighing out the required amount of ester and dissolving in 50 percent aqueous ethanol to make a 0.0395 N solution.

At first, both 0.0395 N base and ester solutions were equilibrated at constant temperature bath and then were mixed by pippetting 10 ml of the base into 10 ml of the ester solution. The timer was started when one half the base was added. The mixture was shaken and returned to the constant temperature bath. At certain time intervals, an aliquot of reaction mixture was taken out, quenched with equal volume of 0.0388 N hydrochloric acid and back titrated with 0.0187 N sodium hydroxide to a phenolphthalein end point. Time was recorded when the one half reaction mixture was added to the acid solution. All esters were purified by preparative gas chromatography and distilled under reduced pressure. All reactions were carried out to at least 60 percent completion.

Calculation of Second-Order Rate Constants

Due to the concentrations of initial base and ester solutions are made up equal so that the rate is proportional to the square of

the concentration of one reactant and expressed by the following equation (Equation 3)

$$-\frac{d\,A}{A^2} = k\,dt \qquad (3)$$

If the concentration is A_o at $t = 0$ and A at time t, integration yields the following equation (Equation 4)

$$\frac{1}{A} - \frac{1}{A_o} = k\,t \qquad (4)$$

Thus a plot of $\frac{1}{A}$ versus t would be linear, with a slope equal to the second-order rate constants. The intercept $\frac{1}{A_o}$ gives initial concentration.

Table 8 and Figure 5 show the data for a typical kinetic run on endo-cyclopropyl endo-ester XXXVIII. Each of the esters was run two or three times. The data put through the computer and the values for the slopes were obtained and averaged.

Measurement of the pKa's of the Cyclopropyl-fused Bicyclo-[2.2.2]-octane Saturated and Unsaturated Acids

The pKa's of various cyclopropyl-fused bicyclo-[2.2.2]-octane

Table 8. Alkaline Hydrolysis of Ester XXXVIII in 50 Percent (Weight) Aqueous Ethanol at 25°C

t (min.)	back titration ml	conc. base A x 10^2	$\frac{1}{A}$
90.94	1.045	1.93	51.96
181.65	1.085	1.86	53.92
272.63	1.098	1.83	54.77
603.78	1.195	1.65	60.67
1321.20	1.352	1.35	73.97
1554.05	1.373	1.31	76.19
2062.80	1.440	1.19	84.31
2785.35	1.520	1.04	96.53
3036.25	1.540	0.997	100.35
3469.23	1.585	0.918	108.99
4207.62	1.625	0.839	119.26
4925.44	1.670	0.760	131.67

Twenty ml of mixed solution containing 10 ml of 0.0395 N base and 10 ml of 0.0395 N ester with one ml aliquot quenched in one ml 0.0388 N HCl and back titration with 0.0187 N base.

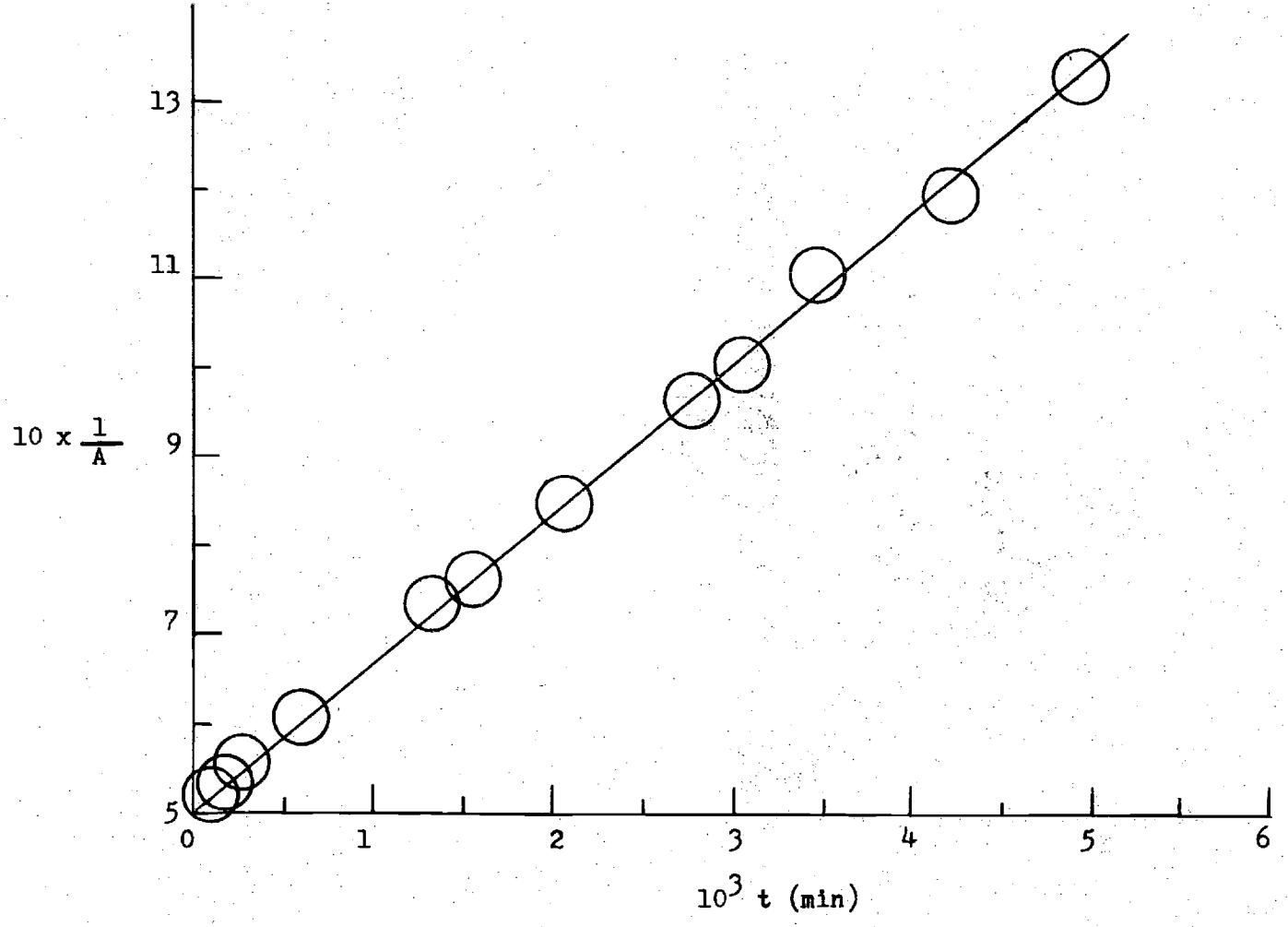


Figure 5. The Second-order Kinetic Plot for Alkaline Hydrolysis of Ester XXXVIII

saturated and unsaturated acids were determined by potentiometric titration in 50 percent aqueous ethanol [42, 43, 44, 45] using a Beckman Model 1019 pH meter with glass and calomal electrodes. The 50 percent aqueous ethanol was made by mixing equal weights of freshly purified water and absolute ethanol.

Standard Solutions

Standard sodium hydroxide solution was prepared by dissolving 0.4 g of sodium hydroxide into one liter 50 percent aqueous ethanol. The solution was standarized by titration with potassium acid phthalate and found to be 0.00971 N.

Buffer solution for calibration of the pH meter was prepared by dissolving 0.0183 g of freshly sublimed benzoic acid in 100 ml of 50 percent aqueous ethanol. The molarity of the acid was found to be 1.5×10^{-3} M by titration with standard base. Benzoic acid/sodium benzoate buffer solution was prepared by mixing exactly one half the volume of standard base required to neutralize 40 ml of the benzoic acid solution. [46]

Freshly recrystallized, sublimed cyclopropyl-fused bicyclic acids were weighed into dry 50 ml volumetric flasks and were added up to the mark with 50 percent aqueous ethanol which had been stored at 25°C.

In each case these solutions were made up to be as close to 1.5×10^{-3} M as possible. The capped volumetric flasks were then stored in the constant temperature bath at 25°C until they were titrated.

Titrations

The titrations were made in a 100 ml tall form beaker which was immersed into the constant temperature bath water deep enough to cover the inside solution. The beaker was fitted with a rubber stopper through which were inserted the electrodes, a nitrogen inlet tube, a NBS thermometer and the tip of the base dispensing burette, and an air driven Teflon encased stirring bar. Nitrogen was slowly charged to the beaker through the titration.

The pH meter was calibrated with the benzoic acid buffer to read 5.738, which is the reported thermodynamic pKa of benzoic acid in 50 percent aqueous ethanol.[47, 48] The pH meter was checked with buffer between each set of measurements to insure against drift. In general, no adjustment was necessary during the titrations which took several hours.

Forty millimeters of the acid solution to be titrated was placed to the tall formed beaker by volumetric pippette. The solution was stirred when standard base was added rapidly from the burette.

The addition was stopped when enough standard base had been added to come within 0.2 ml of the anticipated half-neutralization point of the acid. Stirring was continued until the temperature within the beaker had reached at 25°C. Stirring was then discontinued and the pH of the solution and the volume of standard base added were recorded. This procedure was then repeated with base being added in increments 0.01 ml until a point 0.2 ml beyond the anticipated half-neutralization point was reached.

The equivalent point of the acid solutions were determined by continuing titration. Standard base was added rapidly to a point about within 0.2 ml of the anticipated equivalent point. The pH and volume of base were recorded in increments of about 0.01 ml. The equivalent point was taken as the point where the slope of a pH vs. volume plot is the greatest.

Treatment of data

The Henderson-Hasselbach equation [49] is used to calculate the pKa of the acid. (Equation 5)

$$pKa = pH + \log \frac{[acid]}{[salt]} \qquad (5)$$

This equation is derived from the expression for dissociation constant of the acid. (Equation 6)

$$K_a = \frac{[H^+][A^-]}{[HA]} \qquad (6)$$

The initial concentration of acid can be found from the equivalent point of titration. The concentrations of unreacted acid and formed salt may be calculated from the volume of base used. Once pH at that point is recorded, the pKa of acid may be calculated using Equation (5). The pKa found are then averaged to give a pKa for that run. Table 9 shows the method of calculation for Tricyclo-[3.2.2.0 $^{2.4}$ exo]-nonane-2-exo-carboxylic acid. The pKa's from the measurements of two independently prepared solutions were averaged to give the pKa for each acid and the average deviation. Deviations of pKa for a single point were never more than 0.005 from the average while the average deviation in a single run was usually less than $\pm$ 0.001.

Measurements of the Rates of Solvolysis of the Isomeric Bicyclo-[2.2.2]-octane-2-carbinyl Unsaturated Tosylates, LII and LIV, Saturated Tosylate LVI, and Isomeric Tricyclo-[3.2.2.0 $^{2.4}$]-non-2-carbinyl Tosylates

Table 9. The Calculation of pKa of Tricyclo-[3.2.2.0 ^{2,4} exo]-nonane-6-exo-carboxylic Acid by the Henderson-Hasselbach Equation

base ml	moles salt x 10^5	moles acid x 10^5	ratio $\frac{HA}{A^-}$	log $\frac{HA}{A^-}$	pH	pKa
0.0	0.0	5.9134	--	--	--	--
2.940	2.8547	3.0587	1.0715	0.030	6.780	6.810
2.960	2.8742	3.0392	1.0574	0.024	6.785	6.809
2.980	2.8936	3.0198	1.0436	0.019	6.789	6.808
3.005	2.9179	2.9955	1.0266	0.011	6.796	6.807
3.025	2.9373	2.9761	1.0132	0.006	6.802	6.808
3.045	2.9567	2.9567	1.0000	0.0	6.808	6.808
3.060	2.9713	2.9421	0.9902	-0.004	6.813	6.809
3.080	2.9907	2.9227	0.9773	-0.010	6.817	6.807
3.100	3.0101	2.9033	0.9645	-0.016	6.824	6.808
3.120	3.0295	2.8839	0.9519	-0.021	6.827	6.806
6.090	5.9143	0.0	--	--	--	--
Average pKa 6.808 $\pm$ 0.002						

All five tosylates were prepared as described previously. They were recrystallized from absolute methanol twice (10 ml per gram). Anhydrous acetic acid [50] was prepared by adding 8 ml of pure acetic anhydride to 1 liter of reagent grade glacial acetic acid. The mixture was held under reflux for three hours. The anhydrous acetic acid was distilled under atomosphere pressure, b.p. 115°C.

Standard and Indicator Solutions

The standard perchloric acid in acetic acid was prepared by dissolving the commercial 70 percent aqueous acid in five times its own volume of acetic anhydride and diluting the resulting solution with pure anhydrous acetic acid. [51] The perchloric acid in acetic acid solution was compared with potassium hydrogen phthalate and found to be 0.02029 M. [51]

The sodium acetate solution was obtained by dissolving reagent grade sodium carbonate in anhydrous acetic acid and making the solution up to the volume. [52] This solution was then standarized with standard perchloric acid in acetic acid solution by potentiometric titration and found to be 0.02098 M.

The indicator solution was prepared by dissolving approximately 0.1 g of brom phenol blue in anhydrous acetic acid. The indicator is

colorless in acidic acetic acid solution, dim yellow in neutral solution and brilliant yellow in basic solution.

Rate Measurements [50, 52]

Solutions, 0.02 M, of the five tosylates to be solvolyzed were made up at room temperature in 25 ml volumetric flasks from weighed materials. In a typical run, 0.1542 g of tosylate LVI was placed in a 25 ml volumetric flask, and the flask was filled with the standard 0.02098 M sodium acetate in acetic acid solution. This gives a solution that is 0.02098 M in the bicyclo-[2.2.2]-octane-2-carbinyl tosylate. Approximately 2 ml of this solution was sealed in each of 12 ampoules. The ampoules were placed in a constant temperature bath. At suitable times reaction was interrupted by removing an ampoule and immersing it in ice. The ampoule was then opened when at room temperature and 1 ml-syringe was used to withdraw the sample. Three drops of brom phenol blue indicator were added and the yellow solution was titrated to a colorless end point with the 0.0229 M perchloric acid solution. All reactions were carried out to at least 60 percent completion.

Calculations of First-Order Rate Constants

In solvolysis of the five tosylates, the rate law is expressed

by the following equation. (Equation 7)

$$-\frac{da}{dt} = ka \qquad (7)$$

Where a is the concentration of the tosylate and k is the first-order rate constant.

Integration of Equation 7 leads to Equation 8.

$$2.303 \log \frac{a}{a-x} = kt \qquad (8)$$

Where x is the concentration of the reacted tosylate and a - x is the concentration of the unreacted tosylate. The slope of the plot 2.303 log a/a-x versus time t gives the first-order rate constant. The intercept of the plot is equal to zero.

Table 10 and Figure 6 show the data for a typical kinetic run on bicyclo-[2.2.2]-octane-2-carbinyl tosylate LVI.

Epimerization of the Unsaturated Bicyclic Esters, XLI and XLII the Unsaturated Cyclopropyl-fused Bicyclic Esters, XXXV and XXXVI, and the Saturated Cyclopropyl-fused Bicyclic Esters, XXXVII and XXXVIII, XLIII and XLIV

Table 10. Solvolysis of Tosylate LVI in Anhydrous Acetic Acid at 100°C

time ml	$HClO_4$ titration ml	$(a - x)$ x 10^2	$(\ln \frac{a}{a - x})$ x 10^2
58.46	0.940	1.9073	0.9530
103.06	0.875	1.7754	1.6696
153.56	0.810	1.6435	2.4416
205.83	0.750	1.5218	3.2109
294.97	0.645	1.3087	4.7195
393.81	0.555	1.1261	6.2222
573.64	0.425	0.8623	8.8914
742.93	0.315	0.6391	11.8868
1046.42	0.200	0.4058	16.4288

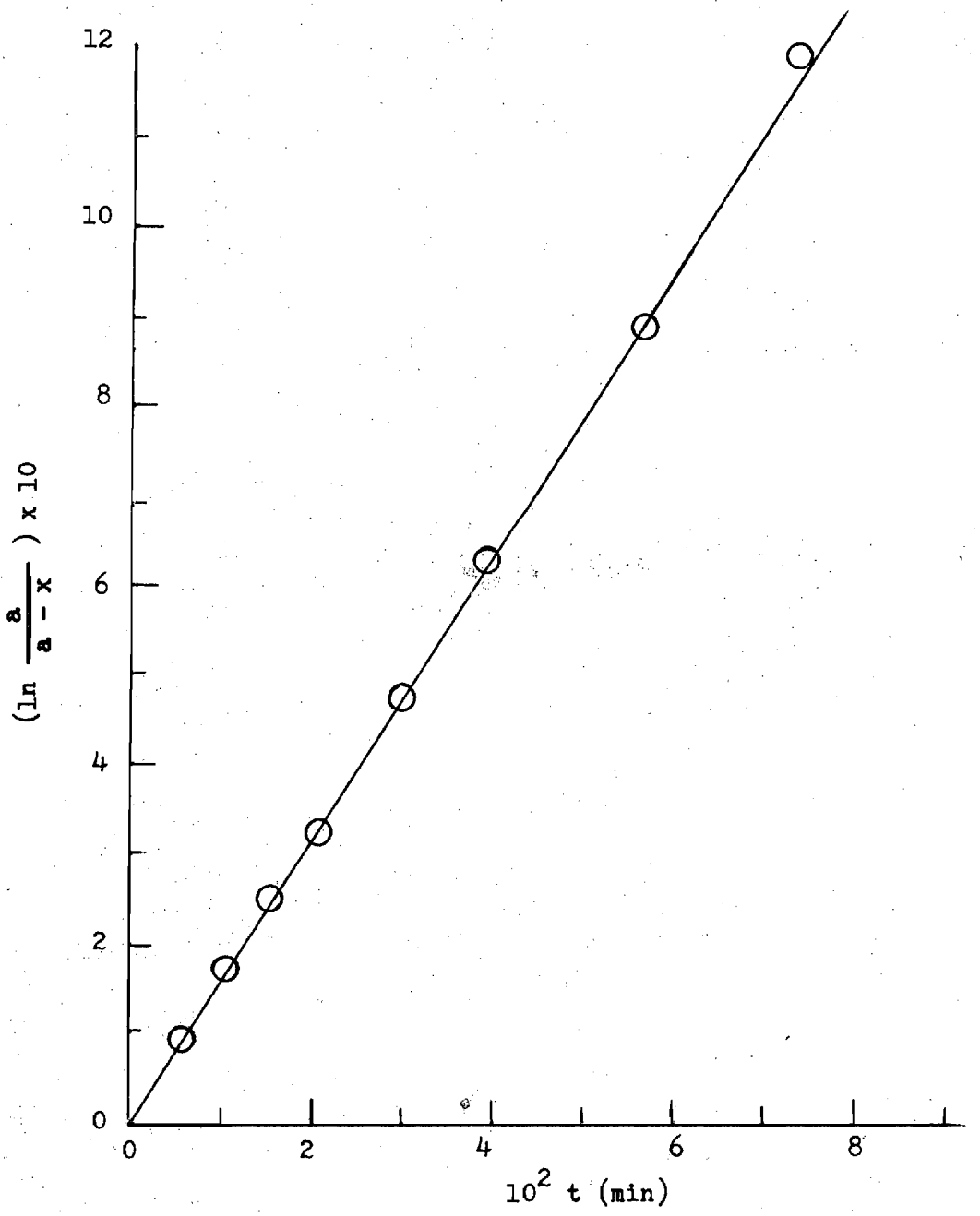


Figure 6. The First-order Kinetic Plot for Solvolysis of Tosylate LVI

To each of eight separate solutions of 0.0288 g (1.25 mg-atoms) of sodium in 2.5 ml of anhydrous ethanol was added 0.22 to 0.24 g (1.25 milli-moles) of the ester.[38] The solution was allowed to stand for two or three weeks, poured into water, acidified with hydrochloric acid, extracted with ether, the ether layer washed with water, dried over anhydrous magnesium sulfate and evaporated in vacuo. The residue was distilled under pressure. Glc (tris-1,2,3-cyanoethoxy-2-propane, 108°C) show two compounds in the various ratios for each pair of epimers.

CHAPTER IV

DISCUSSION OF RESULTS

Table 11 summarizes the iodolactonization of four unsaturated bicyclic acids, XLV, XLVI, LXV and LXVI. After treatment with potassium iodide and iodine in sodium bicarbonate solution, acids XLVI and LXV give iodolactones LXIV and LXIII, but acids XLV and LXVI give no reactions. Both iodolactones LXIII and LXIV show strong infrared absorptions at 1790 cm^{-1} and parent ion peaks at m/e 278 and 290 respectively. The iodolactonization proves that the carboxylic group in XLVI and LXV is endo to the olefin and that in XLV and LXVI is exo to the olefin.

Table 12 shows that six cyclopropyl-fused bicyclo-[2.2.2]-octane carboxylic esters, XXXV, XXXVI, XXXVII, XXXVIII, XLIII and XLIV, have different retention times. These retention times will assist to identify these isomeric compounds and are extremely important for differentiating the epimeric pairs.

In order to prove the stereochemical relations for epimer pairs, we have carried out several epimerizations which were started

Table 11. Iodolactonization of Various Unsaturated Bicyclo-[2.2.2]-octane Acids

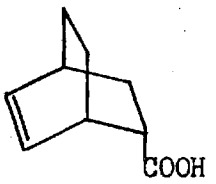
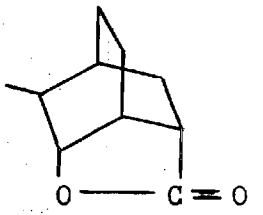
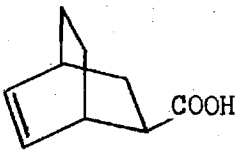
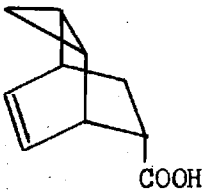
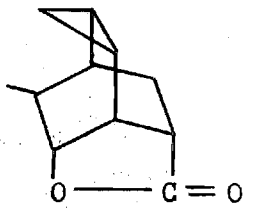
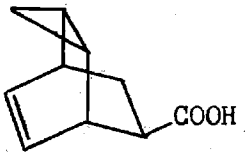
Compound	Iodolactone
 LXV	KI, I_2, $NaHCO_3$ →  LXIII
 LXVI	KI, I_2, $NaHCO_3$ → N. R.
 XLVI	KI, I_2, $NaHCO_3$ →  LXIV
 XLV	KI, I_2, $NaHCO_3$ → N. R.

Table 12. Retention Times for Various Bicyclo-[2.2.2]-octane Derivatives

Compound	Retention Time, min
XXXV	7.04
XXXVI	9.14
XXXVII	9.32
XXXVIII	8.17
XLIII	8.55
XLIV	8.02

Temperature = 108°C; Flow Rate = 40 - 60 ml/min.

from each epimer of the epimer pairs. Table 13 summarizes the percentages of equilibrium mixtures from XLI or XLII, XXXV or XXXVI, XXXVII or XXXVIII, and XLIII or XLIV after two or three weeks equilibrium in sodium ethoxide and ethanol solution at 25°C. We found that both compounds XLI and XLII give the same equilibrium mixture, 69 percent of XLI and 31 percent of XLII. This evidence tells us that the compounds, XLI and XLII are stereochemically related epimers. Same equilibrium mixtures were obtained from the other three epimer pairs XXXV and XXXVI, XXXVII and XXXVIII, and XLIII and XLIV, proves that they are also stereochemically related epimers.

The numbering systems for the protons of cyclopropyl-fused bicyclo-[2.2.2]-octane derivatives are listed in Table 14. The nmr chemical shifts of the individual protons and coupling constants of the corresponding protons for cyclopropyl-fused bicyclo-[2.2.2]-octane derivatives are listed in Tables 15 and 16. In order to extensively study the structures of the compounds XXXV, XXXVI, XXXVII, XXXVIII, XLIII and XLIV, we have applied 100 mhz nmr, double resonance technique and addition of shifting reagents to obtain better resolution and to assign the absoption peak, and also used computer program nmr simulation to confirm the calculating coupling constants.

Table 13. Epimerization of Various Bicyclic and Cyclopropyl-fused Bicyclic Esters

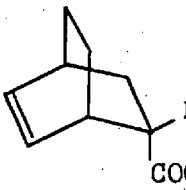
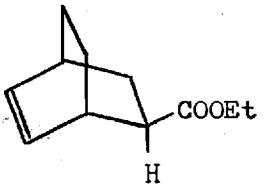
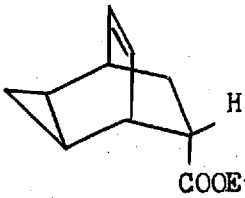
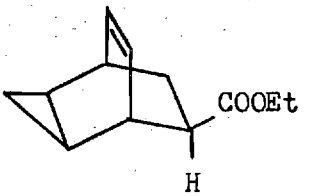
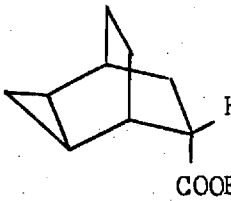
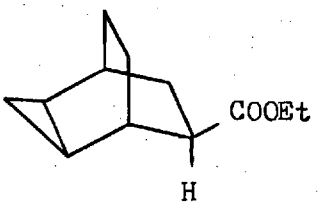
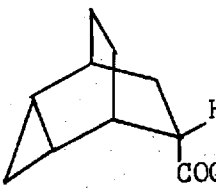
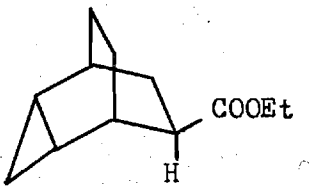
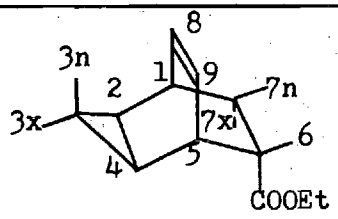
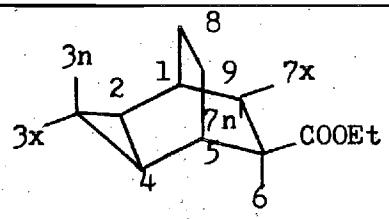
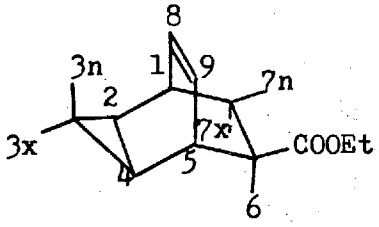
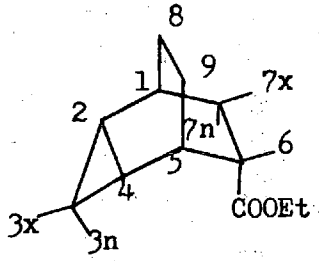
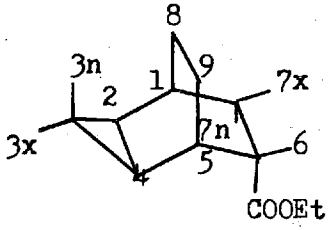
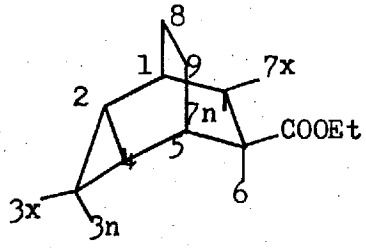
Reactant	Product	Reactant
 XLI	XLI 69% + XLII 31%	 XLII
 XXXV	XXXV 35% + XXXVI 65%	 XXXVI
 XXXVII	XXXVII 58% + XXXVIII 42%	 XXXVIII
 XLIII	XLIII 26% + XLIV 74%	 XLIV

Table 14. The Numbering Methods for Hydrogen Atoms of Cyclopropyl-fused Bicyclo-[2.2.2]-octane Derivatives

Compound	Numbering Method	Compound	Numbering Method
XXXV		XXXVIII	
XXXVI		XLIII	
XXXVII		XLIV	

n = endo; x = exo.

Table 15. Nmr Chemical Shifts for Various Cyclopropyl-fused Bicyclo-[2.2.2]-octane Derivatives

Compound	nmr, τ								
	H_5	H_6	H_{7x}	H_{7n}	H_1	$H_{2,4}$	$H_{8,9}$	H_{3n}	H_{3x}
XXXV	6.83 (m,1)	7.60 (4d,1)	7.89 (4d,1)	8.50 (4d,1)	7.17 (m,1)	9.04 (m,2)	4.10 (m,2)	9.94 (m,2)	
XXXVI	6.81 (m,1)	7.35 (4d,1)	8.24 (m,2)		7.22 (m,1)	9.07 (m,2)	4.22 (m,2)	9.97 (m,2)	
XXXVII	7.71 (m,1)	7.50 (4d,1)	8.38 (4d,1)	7.95 (4d,1)	8.04 (m,1)	9.15 (m,2)	8.70 (m,4)	9.54 (2t,1)	9.77 (2t,1)
XXXVIII	7.78 (m,1)	7.36 (4d,1)	7.91 (4d,1)	8.33 (4d,1)	8.10 (m,1)	9.11 (m,2)	8.73 (m,4)	9.37 (2t,1)	9.67 (2t,1)
XLIII	7.52 (m,1)	7.73 (4d,1)	8.55 (m,1)	8.10 (m,1)	8.02 (m,1)	9.18 (m,2)	8.40 (m,4)	9.55 (2t,1)	9.84 (2t,1)
XLIV	7.73 (m,1)	7.62 (m,1)	8.17 to 8.50 (m,2)		8.08 (m,1)	9.13 (m,2)	8.53 (m,4)	9.53 (2t,1)	9.74 (2t,1)

Table 16. Nmr Coupling Constants for Various Cyclopropyl-fused Bicyclo-[2.2.2]-octane Derivatives

Coupling Constants	Compound				
cps	XXXV	XXXVI	XXXVII	XXXVIII	XLIII
$J_{5,6}$	2.0	2.5	2.3	2.5	2.0
$J_{6,7n}$	10.4	2.5	4.8	11.0	6.3
$J_{6,7x}$	2.5	10.5	10.7	5.0	11.5
$J_{7n,7x}$	12.0	12.5	12.5	12.5	12.0
$J_{7n,1}$	2.8	2.0	2.0	2.5	2.0
$J_{7x,1}$	2.0	2.8	2.5	2.1	2.5
$J_{8,9}$	12.0	12.0	--	--	--
$J_{1,8}$	8.3	7.85	--	--	--
$J_{5,9}$	8.3	7.85	--	--	--
$J_{5,8}$	2.1	2.1	--	--	--
$J_{1,9}$	2.1	2.1	--	--	--
$J_{2,4}$	--	--	10.5	10.5	10.5
$J_{2,3n}$	--	--	3.8	3.8	3.5
$J_{4,3n}$	--	--	3.8	3.8	3.5
$J_{2,3x}$	--	--	7.5	7.5	7.3
$J_{2,3n}$	--	--	7.5	7.5	7.3
$J_{3n,3x}$	--	--	6.0	6.0	6.5

The addition of the compound $Eu(fod)_3$ to the solution of the compounds XXXVI and XXXVII give striking spectral simplification by virtue of reversible complexation leading to pseudocontact shifts.[53,54] Plots of downfield chemical shift versus molar ratio $Eu(fod)_3$/substrate give straight lines for $-CH_2-$, $-CH_3$, vinyl protons, and C-6 protons. Figure 7 shows straight lines for $-CH_2-$, $-CH_3$, vinyl protons and C-6 proton of cyclopropyl-fused bicyclic unsaturated ester XXXVI and Figure 8 shows three straight lines for $-CH_2-$, $-CH_3$, and C-6 proton of cyclopropyl-fused bicyclic saturated ester XXXVII. The individual protons give characteristic shift magnitudes in the order of $CH_2 >$ C-6 $> CH_3 >$ vinyl. In other words, the shift depends upon the distance to the chelate center of the shifting reagent.

There seems to be a rough correlation between the interaction of the cyclopropane ring and the chemical shifts of the neighboring protons.[55, 56] We have observed the nmr spectra of a pair of the compounds, one of which has a cyclopropane ring introducing into the other without any significant alteration in the geometry of the remaining part of molecule. We have compared the nmr spectra of unsaturated bicyclic esters XLI and XLII with those of the corresponding unsaturated cyclopropyl-fused bicyclic esters XXXV and XXXVI which differ from

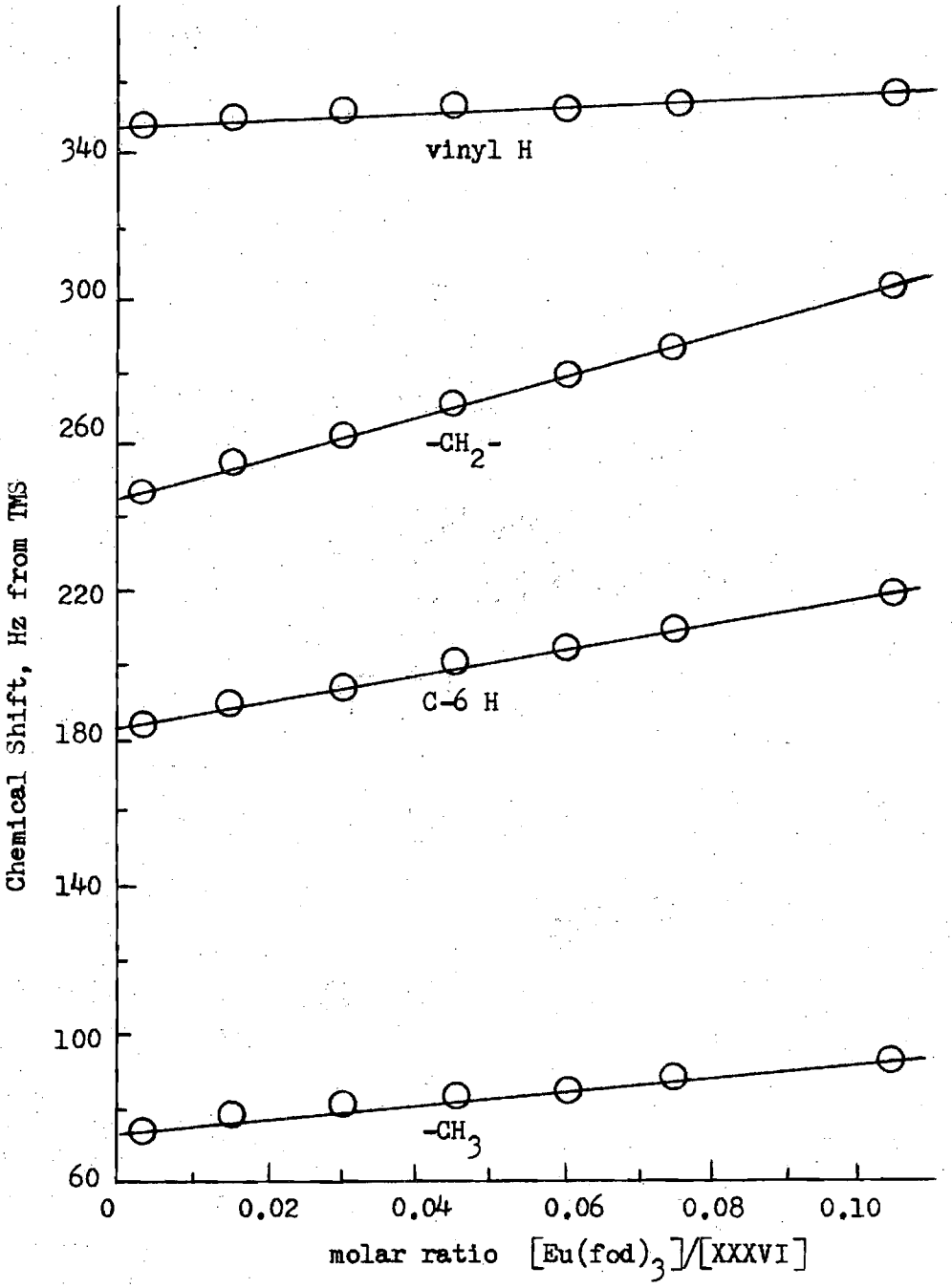


Figure 7. Variation of Induced Shift With Molar Ratio $[Eu(fod)_3]/[Substrate]$ for Tricyclo-[3.2.2.$0^{2.4}$endo]-non-8-ene-6-exo-carboxylic Ester XXXVI

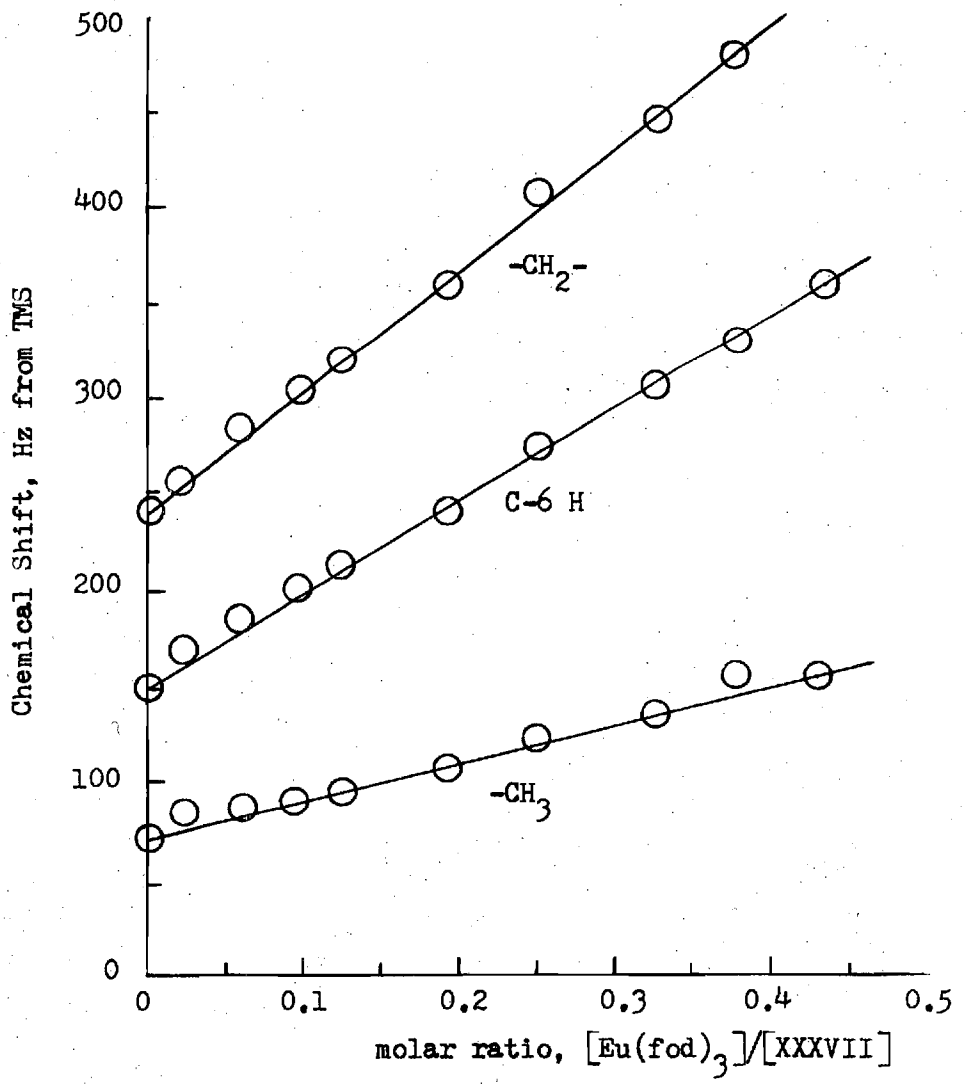


Figure 8. Variation of Induced Shift With Molar Ratio [Eu(fod)$_3$] /[Substrate] for Tricyclo-[3.2.2.0 $^{2.4}$ endo]-non-6-endo-carboxylic Ester XXXVII

the two former esters only in lack of the cyclopropane methylene. Table 17 shows the nmr spectra data on these four esters XLI, XLII, XXXV and XXXVI, and the values of additional signal shifts arising from the long-range shielding effect of the introduced cyclopropane ring in XXXV and XXXVI. In compound XXXV, two bridgehead protons H_a, H_d, shift 0.53, 0.57 respectively to the downfield and the vinyl protons H_b, H_c, shift 0.2 to the upfield. In compound XXXVI, same results were obtained, two bridgehead protons H_a, H_d, shift to the downfield by 0.33, 0.39 respectively and the vinyl protons H_b, H_c, shift to the upfield by 0.32 . Thus the anisotropic of the shielding effect of a cyclopropane ring is apparent in the cyclopropane ring containing unsaturated bicyclic esters.

The rates of alkaline hydrolysis of the isomeric 5,6-cyclopropyl-fused bicyclo-[2.2.2]-octane-2-carboxylic esters in 50 percent (by weight) aqueous ethanol have been determined. Table 18 summarizes the results along with the calculated $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values at 25°C. In comparing the relative rates, the rates of the compounds XXXVII, XXXVIII, XLIII, and XLIV are slightly slower than that of their parent compound LXVII. Compound XLIII reacts much more slower than LXVII because the steric hidrance on the bottom of the ring. The compounds XXXVII,

Table 17. Nmr Spectral Data on Tricyclo-[3.2.2.0 $^{2.4}$]-nonane and Bicyclo-[2.2.2]-octane Derivatives

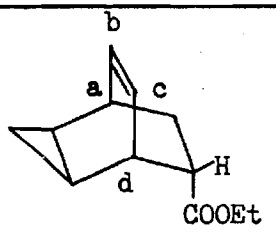
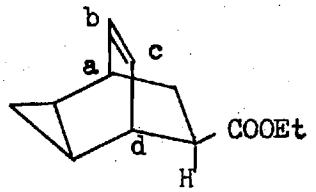
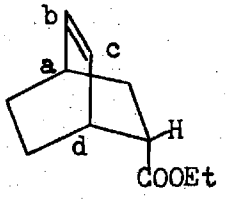
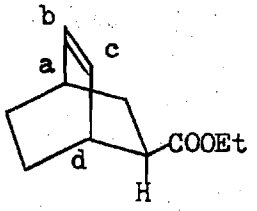
Compound	Assignable Protons	Chemical Shifts Values	Additional shift value due to the cyclopropyl ring ppm
 XXXV	H_a	7.17 (m)	-0.53
	H_d	6.83 (m)	-0.57
	H_b (H_c)	4.10 (m)	+0.20
 XXXVI	H_a	7.22 (m)	-0.33
	H_d	6.81 (m)	-0.39
	H_b (H_c)	4.22 (m)	+0.32
 XLII	H_a	7.70 (m)	---
	H_d	7.40 (m)	---
	H_b (H_c)	3.90 (m)	---
 XLI	H_a	7.55 (m)	---
	H_d	7.20 (m)	---
	H_b (H_c)	3.90 (m)	---

Table 18. Alkaline Hydrolysis Rates for Various Bicyclo-[2.2.2]-octane Derivatives

Compound	Temp °C	k x 10^2 $M^{-1}min^{-1}$	$\Delta H^{\ddagger}_{25}$° kcal/mole	$\Delta S^{\ddagger}_{25}$° cal/mole-K°	$k_{rel,25°}$
LXVII	40	6.68 ± 0.13			
	25	2.16 ± 0.003	13.4 ± 0.8	-29.5 ± 1.0	1.0
XLII	40	7.59 ± 0.14			
	25	2.75 ± 0.01	12.0 ± 0.8	-33.7 ± 1.0	1.3
XLI	40	12.3 ± 0.4			
	25	4.53 ± 0.03	11.8 ± 1.0	-33.4 ± 1.7	2.1
XXXV	40	6.89 ± 0.18			
	25	2.07 ± 0.03	14.3 ± 1.1	-26.5 ± 1.8	0.95
XXXVI	40	11.6 ± 0.3			
	25	3.20 ± 0.09	15.3 ± 1.1	-22.1 ± 1.7	1.5
XXXVII	40	5.91 ± 0.21			
	25	1.72 ± 0.03	14.7 ± 1.2	-25.6 ± 2.3	0.8
XXXVIII	40	5.73 ± 0.17			
	25	1.65 ± 0.03	14.8 ± 1.2	-25.2 ± 2.1	0.76
XLIII	40	1.16 ± 0.03			
	25	0.25 ± 0.008	18.4 ± 1.3	-16.9 ± 2.5	0.12
XLIV	40	4.68 ± 0.11			
	25	1.23 ± 0.03	15.9 ± 1.2	-22.0 ± 2.1	0.57

XXXVIII and XLIV have a slightly different rates due to the non-conjugated electrostatic effects (field effects) or the rates should be equal for all the three compounds since the sigma bonds intervening between the cyclopropyl ring and the reaction center are the same. The compounds XLI and XLII reacts faster than their parent compound LXVII due to the fact that the double bond in XLI or XLII withdraw the charge from the reaction center through the sigma bonds and stabilize the anion formed in the transition state at the carboxylic group. On the other hand, the fact that cyclopropyl-fused unsaturated bicyclic esters hydrolyze slower than the unsaturated bicyclic esters, such as, compound XXXV reacts slower than compound XLII and compound XXXVI hydrolyzes slower than compound XLI, is consistent with the fact that the saturated cyclopropyl-fused bicyclic esters XXXVII and XXXVIII which show slower reactivities than their parent compound LXVII. All the evidence confirms that the cyclopropane ring in this particular bicyclo-[2.2.2]-octane system is an electro-donating group.

The pKa values of the corresponding isomeric acids have been determined in 50 percent (by weight) aqueous ethanol at 25°C and are listed in Table 19. The unsaturated bicyclic acids LXV and LXVI are more acidic than their parent acid LXVIII due to the fact that

Table 19. pKa Values of Various Bicyclo-[2.2.2]-octane Derivatives

Acids	pKa
XLV	6.731 ± 0.005
XLVI	6.576 ± 0.004
XLVII	6.776 ± 0.004
XLVIII	6.810 ± 0.004
XLIX	6.786 ± 0.004
L	6.851 ± 0.005
LXV	6.606 ± 0.005
LXVI	6.554 ± 0.005
LXVIII	6.772 ± 0.006

the unsaturation in the acids LXV and LXVI contribute the electron-withdrawing effect to the reaction center. The saturated cyclopropyl-fused bicyclic acids, XLVII, XLVIII, XLIX and L are less acidic than their parent acid LXVIII due to the fused cyclopropane rings in the structures of XLVII, XLVIII, XLIX and L have the electron-donating effect on their reaction centers. The unsaturated cyclopropyl-fused bicyclic acid XLV is less acidic than the unsaturated bicyclic acid LXVI also proves the fused cyclopropane ring in this bicyclic system is an electron-donating group. However, the unsaturated cyclorpopyl-fused bicyclic acid XLVI is more acidic than the unsaturated bicyclic acid LXV, we have not found an an appropiate reason to explain this yet. There might be some correlation between the carboxylic group and the vinyl group in the structure of XLVI.

All the pKa values of these acids are proportional to the rate constants from the alkaline hydrolysis of the corresponding esters. A plot of pKa's of the tricyclic and bicyclic acids versus the log k_{rel} of alkaline hydrolysis of the ethyl esters of the tricyclic and bicyclic derivatives is shown in Figure 9. It can be seen from the figure that the steric and electronic environment for both the pKa's of the acids and the rates of alkaline hydrolysis of their esters are

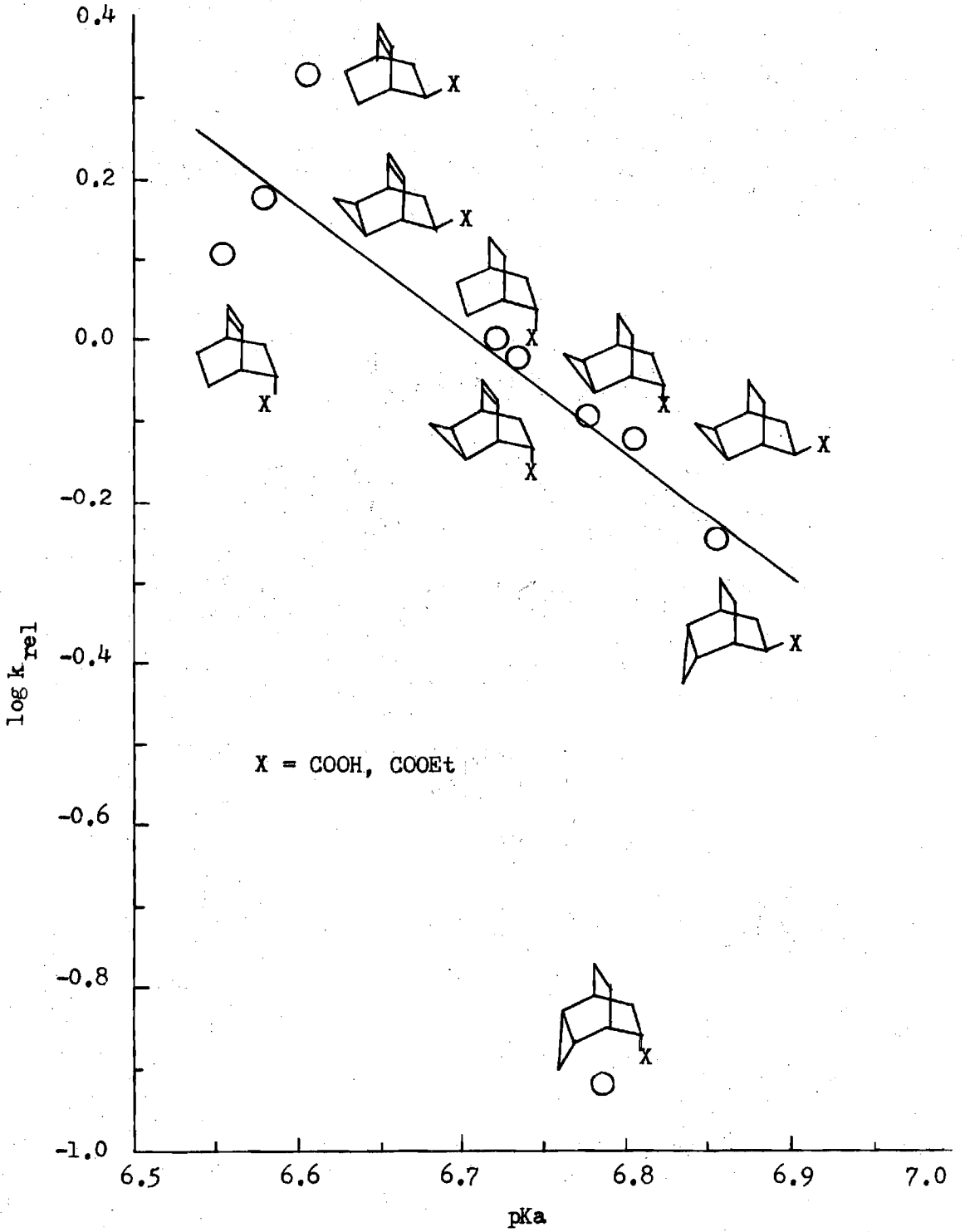


Figure 9. PKa of Various Bicyclic Acids vs. log k_{rel} of Alkaline Hydrolysis of Various Bicyclic Esters

similar except compound XLIII falls off the line due to the steric effects between the hydrogen atom of the cyclopropane and the carboxylic group.

Table 20 summarizes the first order rate coefficient for the solvolysis of the corresponding tricyclic and bicyclic tosylates in anhydrous acetic acid at 75°C and 100°C and along with $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values at 100°C. The solvolysis of unsaturated bicyclic tosylates, LVI and LIV, slower than their parent tosylate LII proves that the vinyl group is an electron-withdrawing group. However, there is no participation effect involved in the solvolysis or the compound LVI should react faster than the compound LIV does. On the other hand, the saturated cyclopropyl-fused bicyclic tosylates, LIX and LXII react faster than their parent compound LII. Therefore again in the solvolytic reactions, the fused cyclopropane in bicyclo-[2.2.2]-octane system is proved to be an electron-donating group. The tosylate LIX react faster than the tosylate LXII is due to the cyclopropyl bend bond toward to the reaction center in the structure of LIX, and gives the assistance to the reaction center in the transition state.

A plot of log k_{rel} of the solvolysis rates versus log k_{rel} of alkaline hydrolysis rates for the tricyclic and bicyclic derivatives

Table 20. The Rate Constants for Solvolysis of Various Bicyclo-[2.2.2]-octane Derivatives

Compound	Temp °C	$k \times 10^4$ min^{-1}	$\Delta H^{\ddagger}_{100^\circ}$ kcal/mole	$\Delta S^{\ddagger}_{100^\circ}$ cal/deg-mole	$k_{rel,100^\circ}$
LII	100	15.8 ± 0.2	26.8 ± 0.3	-8.7 ± 0.4	1.0
	75	1.12 ± 0.02			
LIX	100	36.0 ± 0.2	27.0 ± 0.3	-6.5 ± 0.7	2.28
	75	2.45 ± 0.05			
LXII	100	24.2 ± 0.3	26.7 ± 0.1	-8.1 ± 0.2	1.53
	75	1.70 ± 0.03			
LVI	100	4.52 ± 0.09	27.1 ± 0.4	-9.7 ± 1.1	0.29
	75	0.303 ± 0.006			
LIV	100	7.41 ± 0.15	27.3 ± 0.5	-8.8 ± 1.7	0.47
	75	0.486 ± 0.010			

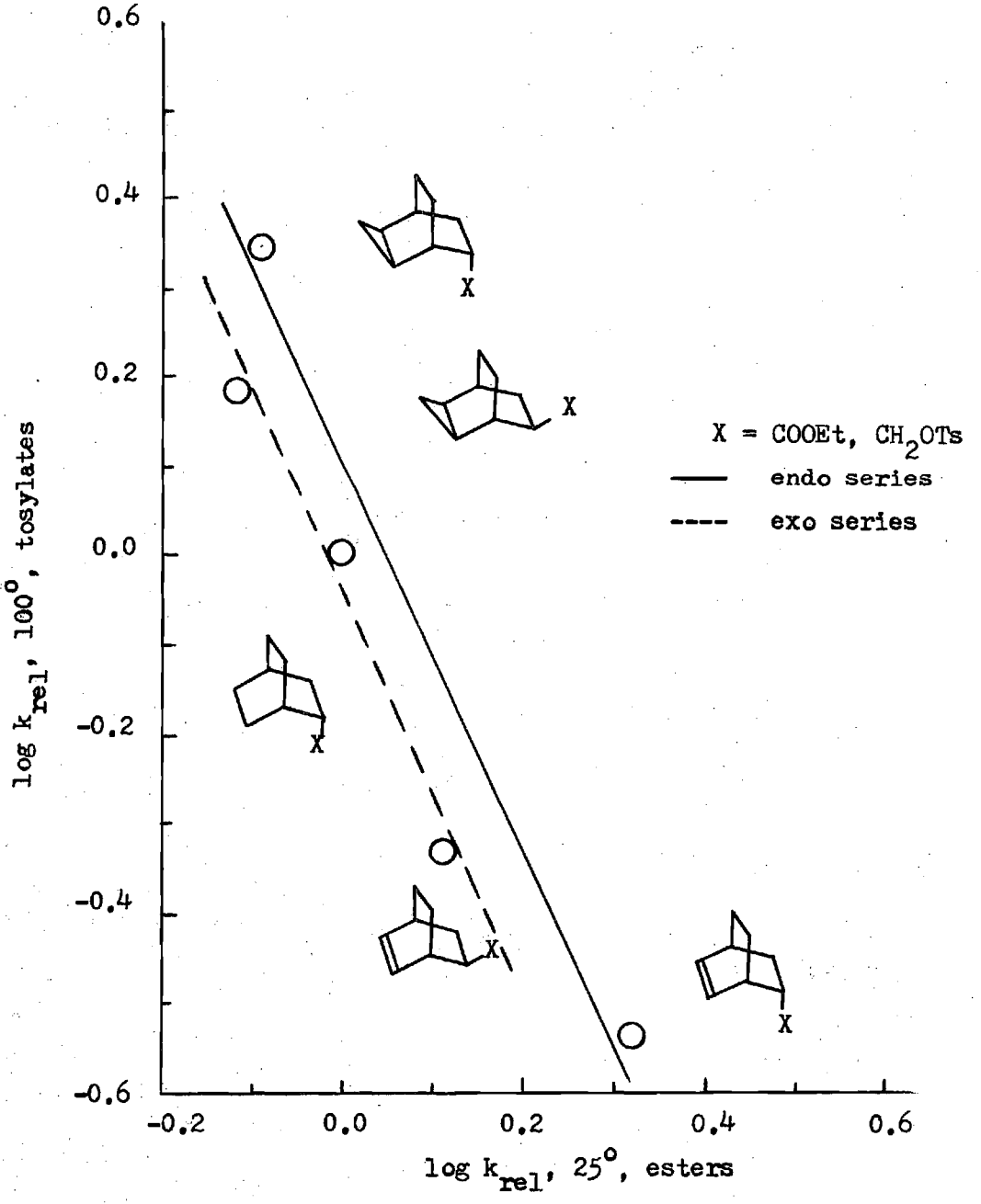


Figure 10. log k_{rel} of Alkaline Hydrolysis of Various Bicyclic Esters vs. log k_{rel} of Solvolysis of Various Bicyclic Tosylates

is shown in Figure 10. It gives a roughly linear correlation except compound LIX falls off the line perhaps due to the participation effect.

A plot of the pKa's for the tricyclic and bicyclic acids versus the solvolysis rates of the tricyclic and bicyclic tosylates is shown in Figure 11. It also gives a linear correlation except compound LIX falls off the line due to the participation effect.

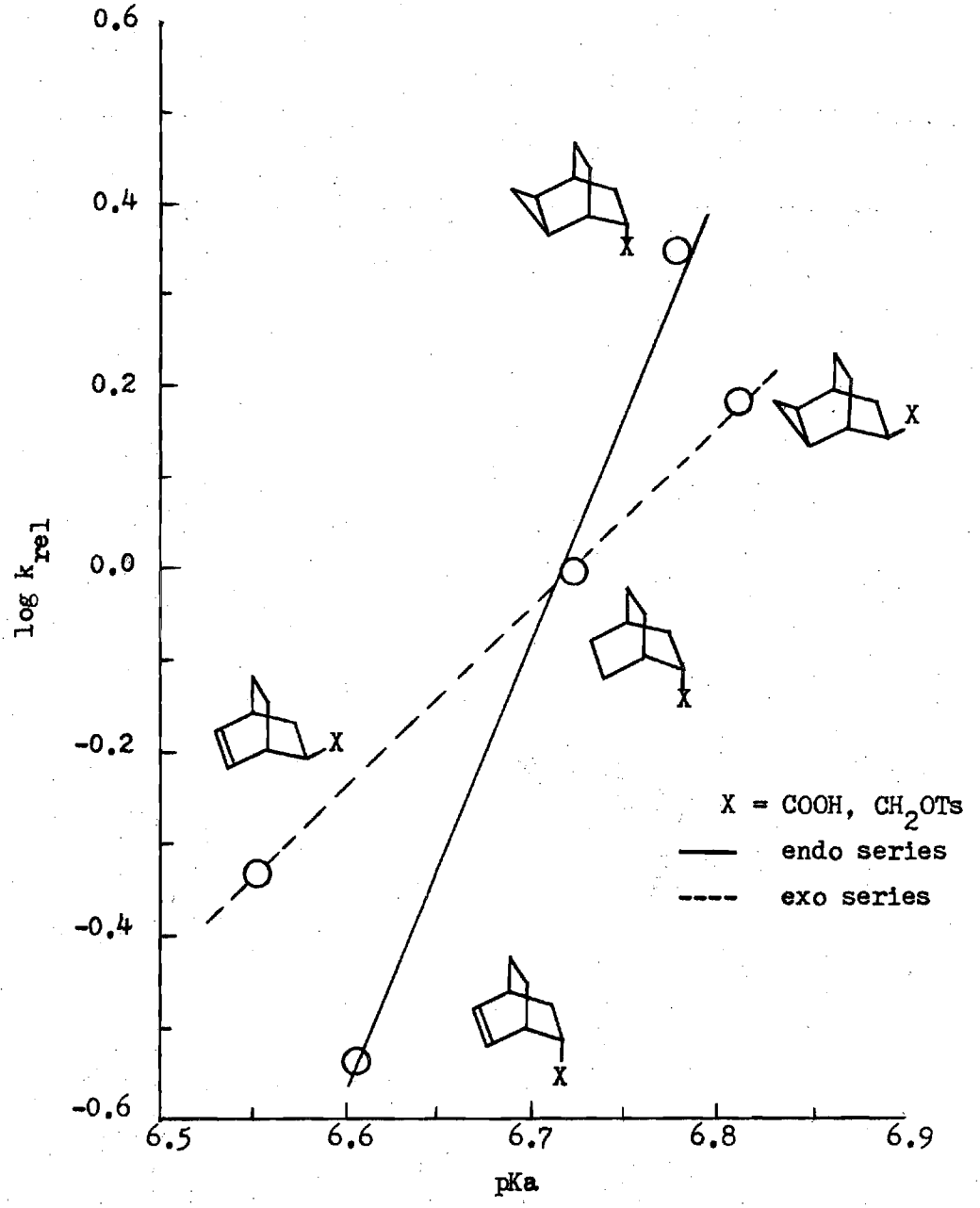


Figure 11. log k_{rel} of Solvolysis of Various Bicyclic Tosylates vs. pKa of Various Bicyclic Acids

CHAPTER V

CONCLUSION

The analysis of the reactivities of various reactants reveals that: (1) the cyclopropane ring in bicyclo-[2.2.2]-octane system has a small non-conjugated electrical effect on the reaction center and the magnitude of which depends on the orientation of the cyclopropane ring with respect to the reaction center; (2) the cyclopropane ring in bicyclo-[2.2.2]-octane system is an electron-donating group which is contrary to the published literature.

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